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SOME HIGHLIGHTS OF THE EARLY HISTORY OF CHICAGO

J. R. LINDSAY
Chicago, Ill., U.S.A.

Some of you are well acquainted with America and the Chicago region from previous occa ions but many of you are here for your first visit. We hope that you will all have pleasant and interesting time In the next few days we hope to show you some of the places of interest in Chicago and it surroundings. By way of introduction to this region I propose to review for you some of the highlights of Chicago s early development.

Early in the 16th century J ques Cartier of France first explored the St. Lawrence River Valley and in 1534 reached the Lachine Rapids, at what is now Montreal. The French were interested mainly in fisheries nd the fur trade In the lat 16th and 17th centuries colonization of the North Carolina, Virginia nd the Massachusetts Bay reas was dev loping but was limited to the east of the mount in until early in the 18th century The Spanish had already arrived in Florida nd had small colony at St. Augustine

In the 17th c ntury colonization of "New France under Champlain and Cardinal Richelieu was slowly progressing E plorations continued westward to the upper end f Lakes Huron and Michigan eventually to extend down the Mississ ipp River t th Gulf of Mexi o Fren h missions were established at St. Ignace nea Ma kinac Island and in 1600 on the shores of Lake Superior

The first whit men t set eyes on the sit of future Chicago were a French-born Jesu t, Father Jacques Marquette and Canadian explorer and map-maker Lou Joli et, with five ca oe men or voyageurs in 1673 They were looking for the M ssissippi River which they knew only by legend thinking it might lead to the fabulou riches of the Orient. The route f llowed by them took them cross Lak Michigan int Green Bay and along the Fox and Wisconsin rivers, to the Mississippi, then down far the Arkansas River At this point they turned, fearing tta k by Indians, paddled back nd entered the Illinoi River This they followed until th y came to large Indian illage near what i now the city of Ottawa, Illinois. These I dian were friendly and guided th m up to the Des Plaines Ri er fr m whi h they crossed the low lying land to the Chicago Ri er which flowed int Lak Michigan. From there they paddled north to Green Bay d returned t the r starting point. Th Des Plaines Ri er flowing to the Gulf of Mexico and th Chicago River fl wi g into Lake Michiga were only a few m les part, separated by Mud Lake which at some season formed almost a continuous waterway and an ea y portage The rout o er this portage wa to be util zed b traders for the ext quarter of a century

Marquett promised th Indians to return the f llowi g ear and did so spending the winter in log cabin on the bank of the Chicago River

I 1677 R bert Rene Cavalier ieur de la Salle later known a La Salle persuaded Frontenac the Governor of New France at that time to grant per m ssio t explore the Mississippi Valley further

H and his party came across from New France (Canada) by way of the Niagara Peninsula, orthern Ohio, and Lake Michigan t th Chicago River They crossed the portage t the Des Plaines Ri er and proceeded down the Mississippi.

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the chief who had been given a silver medallion by Washington after the Revolutionary War formally returned the gift, indicating the displeasure of the Indian tribes. The reasons for their hostility to the Americans was not clear

Orders came to evacuate Ft. Dearborn and remove the inmates to Fort Wayne

William Wells was a white man wh had been captured and raised from childhood by Little Turtle, Chief of the Mi mi Indians, and married into his family He was greatly respected by the Indian and was selected to bring a band of thirty Miami' to Ft. Dearborn to guide th inmates t Ft. Wayne Wells advised against attempted withdrawal from the fort, fearing ttack by the hostile Potawatomies under Bla k Partridge and other tribes. H wev r he was persuaded by Captain Heald then in charge to set out with the inmates on the trek to Ft. Wayne. They started out along the Lake Shore but were attacked within a few miles of the fort and all were either killed or captured W lls wa on f the first to be killed. On recognizing whom they had killed according to legend two Indi n leaders removed his heart, divided and te it, hopi g thereby to acquire some of his bravery The step-daughter of Kinzie the respected friend of the Indians, was saved from death t the hands of a Indian warrior A statue showing Black Partridge sa ing the lif of Kinzie step-daughte from the Indian has been preserved and is now located in Lincoln Park in Chicago. The original fort was burned nd nothing further is known of the region until the second f rt was built four years later Although the war of 1812–16 was o er and the fort rebuilt settlers did not come into the northern Illin is area because of hostile I dian tribes, until fter the Black Hawk Wars.

The Black Hawk Wars

Black Hawk was a chief of th F and Sauk tribes, whose sacred burial grou d wa at Rock I land Illin is, I the Missi sippi Ri er They had already withdrawn cross the Mississippi River t Iowa but Black Hawk objected to the ceding of northern Illi ois to the whites by fi other chiefs—some four years earlier without greement by the F x and Sauk tribes. He led his warriors back t Illin is and the Black Hawk W ensued in 1832. The war lasted nly three months, endi g with the Battle f Bad Axe nea the Wisco sin-Illinoi border

By th Treaty f the Grand Council in Chicago in 1833 Black Hawk agreed to remain west f the Mississippi, nd northern Illinoi was open to white settlers.

A statue f Indian by Loredo T ft, the sculptor now verlooks the Rock R e at Oregon Illi is, erroneously said to ha e been a statu f Black Hawk. Southern Illi is wa lready well settled. Illin is had become a sta! In 1818 and n w settlers poured into th n rthern part.

The Illinois Michigan Canal

Meanwhile Chicago was growing nd was incorporated a a town in 1833 with a population f 250 d received it first charter as city in 1837

The eed for canal connecti g Lake Michigan with the waterway to the Gulf f Me ico had been recognized by the early e plorers and was emph ized by the w of 1812 16 as means of movi g wa equipment

The Illinois-Mi higan Can l wa event lly started in 1837 and was completed in 1848. The Chicago River was thereby straightened to it present course at the

La Salle s associate Tonty an Italian known as the man with "the iron hand" one hand having been replaced by an iron hook remained in the Mississippi Valley building forts at Creve Coeur Kaskaskia and Starved Rock (Fort St Louis) while La Salle returned to seek permission to proceed further In 1678 he reached the Gulf of Mexico and claimed the territory for Louis XIV thereby establishing the Louisiana Territory

After 1700 hostile Indians blocked the portage at the Chicago River and nothing is known of the region until after 1780 when Jean Baptiste Point du Sable established a trading post on the north bank of the Chicago River near the lake

At the mid point of the 18th century the map of North America shows the British in possession of the eastern coastal area from the Carolinas to Maine but limited by the Allegany Mountains. The French held Cape Breton Canada northern Ohio and the broad Mississippi Valley down to the Gulf of Mexico. The Spanish held Florida Mexico and part of the southwest leaving the large area west of the Mississippi Valley unexplored In 1759 the British took Quebec and the Treaty of Paris in 1763 ceded Canada to the British The Louisiana Territory including the Mississippi Valley remained a French possession

The Revolutionary War did not extend to the Mississippi Valley because of the intervening mountains. However Clark obtained permission from Patrick Henry Governor of Virginia to travel west but was afforded no help Clark proceeded westward and captured Fort Kaskaskia but for the next four years there were Indian wars preventing further advance westward These wars ended at the Battle of Fallen Timbers, won by Anthony Wayne known as "mad Anthony" This was followed by the Treaty of Greenville at Fort Greenville in eastern Ohio with Little Turtle Chief of the Miami Tribe

This treaty besides opening most of Ohio to white settlement ceded a six mile-square area the present center of the City of Chicago to the U.S The tract was never formally surveyed but it was a momentous real estate transaction in the history of Chicago

Meanwhile Jean Baptiste Point du Sable had proven to have unusual talents He had already established an elaborate trading post on the north bank of the *Chicago River in the early seventeen eighties—with barns, a powered horse mill,* many cattle hogs, poultry and sundry equipment according to the inventory as well as a colletion of paintings.

Fort Dearborn

The first Fort Dearborn ordered by the War Department in 1803 was built on the south bank of th Chicago River Lt. James Strode Swearinger brought the first infantry overland from Detroit and Captain John Whistler grandfather of Whistler the artist, was put in charge

The same year Napoleon sold the Louisiana Territory for 15 $^1/_2$ million and other considerations which concerned settlements with the Spanish

John Kinzie a silversmith and by avocation a fur trader came to Ft Dearborn in 1804 He spoke 7 Indian dialects He bought the house built by du Sable and became popular with the Indians in the region

In 1812 war broke out with England Canada had then been under British control since the Peace of Paris in 1 63 The Indians in the region of the mid west favored the side of the British and became hostile Black Partridge one of

the chief who had been given a silver medallion by Washington after the Revolutionary War formally returned the gift, indicating the displeasure of the Indian tribes. Th reasons for their hostility to the Americans was not clear

Orders came to evacuate Ft. Dearborn and remove the inmates to Fort Wayn

William Wells was a white man who had been captured and raised from childhood by Little Turtle Chief of the Miami Indians, and married into his family He was greatly respected by the Indians and was selected to bring a ba d of thirty Miami's to Ft. Dea born to guide the inmates to Ft. W yne Wells advised against attempted withdrawal from the fort, fearing attack by the hostile Potawatomies under Black Partridge and other tribes. However he was persuaded by Captain Heald, than in charge to set out with the inmates on th trek to Ft. Wayne They started out along the Lake Shore but were attacked within a few miles f the fort and all were either killed or captured Wells was one of the first to be killed. On recognizing whom they had killed according to legend two I dian leaders removed his heart, divided and ate it, hoping thereby to acquire some of h s bravery The step-daughter of Kinzie the respected friend of the I dians, wa saved from death at the hands of an I dian warrior A statue show g Black Partridge savi g the lif of Kinzie s step-daughter from the Indian has bee preserved nd is now located in Lincoln Park in Chicago. The original fort w burned and nothing further is known of the region until th second fort wa built four years later Although the war of 1812–16 was over and the fort rebuilt, settlers did not come into the northern Illinois area because of hostile I d an tribes, until after the Black Hawk Wars.

The Black Hawk Wars

Black Hawk was hief f the Fo and Sauk tribes, whose sacred burial ground was at Rock Island Illinois, in the Missi sippi R er They had already w thdrawn cros th Mississipp River t Iowa, but Black Hawk bjected to the ceding f northern Ill ois to the whites by f e ther chi fs—some four years earlier without greement by the Fo nd Sauk tribes. He led his warriors back t Ill n i nd the Black Hawk War en ued in 1832 The wa lasted only three months, end ng with the Battle of Bad A e near the Wiscon in Illinoi border

B the Tre ty f the Grand Coun il in Ch cago in 1833 Black Hawk agreed to emain west f the Mi sissippi and northern Illino wa pen to white settlers. A statue of n Ind n, by Lored Taft, the sculptor now overlook th Rock R er at Oregon Illin is, erroneou ly said t ha e been statue f Black H wk. Southern Illinois wa already w ll settled. Illin is had become a st te i 1818 and now settlers poured int the north rn part.

The Illinois-Michigan Canal

Meanwhil Chicago was growing nd was incorporated as town in 1833 with a population of 2_0 and recei ed it first harter as city in 183

The need for a can l con ecting Lake Michigan w th the w terway to the Gulf f M xico had been recognized by the ea ly e plorers d wa emphasized by the war of 1812–16 as mean of moving wa equ pment.

The Illinois-Michigan Canal wa eventually started in 1837 and was completed in 1848 The Chicago River wa thereby straightened to its present course at the



F 1 Chicag in 1833 Th juncti n f th n rth nd outh bran hes f th Chi g Ri

entrance from Lake Michigan The canal was later deepened and the locks permitted the flow of water to be reversed Navigation was established from the *Lake to the Gulf of Mexico—and the avoidance of pollution of the lake from* Chicago's sewage was made possible. The canal was an important factor in the early development of Chicago It brought produce from the valley of the Illinois River to Chicago and distributed merchandise from the East to the river towns and the interior The population rose from 20 000 in 1848 to 75 000 within six years and commerce expanded in proportion

Although the canal made navigation possible its effect was soon overshadowed by the development of railroads. The first few miles of track of the Galena and Chicago Union Railroad eventually to become the Chicago and Northwestern system opened in the same year The first locomotive to reach Chicago the Pioneer built by the Baldwin Locomotive Works in Philadelphia i still in the possession of the Chicago and Northwestern railway Chicago rapidly became a transportation center and within 12 years there were already eleven trunk lines coming into the city

Raising of the Grades

One of the important early developments in Chicago was the raising of the grades" Chicago had been built on low land and in wet weather the streets were

of mud and basements flooded. The story is told that on Lake Street one day a man head was noticed protruding from the mud in the middle of the street. On being politely asked if he needed some help he responded No thank you, I am riding n my horse

From 1855–1860 under the influence of George Pullman an engineer later to develop the great Pullman Ca Company Chicago was raised ut of the swamp Sidew lks and street had t be raised as much as four to eight feet nd a drain ge system developed One large hotel was raised eight feet by the use of 2,00 jackscrews, reputedly "without spilling even a cup f tea

A significant event of the period i Chicago was th seco d national conven tion of the Republican Party i 1860 when it nomin ted its first president thereby st rting great American Abraham Linc ln, on the way to immortality

Other developments were the completion of the city's first waterworks in 1865 of which the water tower still stand on North Michigan Avenue the open ing f th Chicago stocky rd in th same year and the entry of the Illinoi Central Railroad into Chicago alo g the lak front The first Ru h Medical College building was in iste ce

The Chicago Fire of 1871

The Great Chicago F re took place i early October of 1871 Almost no rain had fallen for over three months and the w lls were dry The fire tarted in the O'Leary Barn but ot l gend has it by the cow kicking er the la tern The fire raged out of control.

The entral part of Chicago includi g the business district was a complete ruin. 300 people died and of Chicago 335,000 inhabita ts 90,000 were left homeless.

Pla f rebuilding were begun at once Temporary structures were built and within few years permanent rebuilding had progressed so that few traces of the catastroph could be found

Rush Medical College continued in a temporary bu lding for f ur years and was rebuilt in 1875 th building being replaced n 1924 by the Rawson Building.

The First Skyscraper

T Chicago rch tect W L. B. Jenn y goes the credit for designing the first skyscraper I ll earlier build ngs th walls had carried the w ight f the structure As the b ildi gs rose height th piers t th ground had to be mad thick Ten st es called for w lls four feet thick t the base d thi was the practical l mit

Jenney des gned a iro skeleton f columns, girders a d beam t support the roof floors d walls. Valuable space formerly given o er to heavy masonry was thereby sa ed and the walls could even be mad of glass if desired Th new method was used in the Home Insurance Building, built n 1884 and revolutionized the construction ind stry A brilliant era in structural engi eeri g and the modern skyscraper were to f llow



Fig 1 Chicag in 1833 Th juncti n of th north and south branches of the Chi ag Riv

entrance from Lake Michigan The canal was later deepened and the locks per mitted the flow of water to be reversed Navigation was established from the Lake to the Gulf of Mexico—and the avoidance of pollution of the lake from Chicago s sewage was made possible The canal was an important factor in the early development of Chicago It brought produce from the valley of the Illinois River to Chicago and distributed merchandise from the East to the river towns and the interior The population rose from 0 000 in 1848 to 75 000 wihin six years and commerce expanded in proportion

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THE CRYSTALLOGRAPHIC STRUCTURE AND MINERALIZATION OF OTOSCLEROTIC BONE

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An analysis is presented of more than 200 bone samples. In addition different crystallic forms are compared with the results obtained by the microradiographic method.

In our preceding study concerning the crystallic structure of otosclerotic bone, three types of structures were defined:

1. One which corresponds to the structure of normal human bone.
2. One with no distinctly observable crystallic structure.
3. One clearly diverging from the structure of normal human bone.

A detailed analysis of these results was carried out; the distribution of the material is demonstrated in Table 1.

TABLE 1. *Crystallic structure of 210 samples.*

Structure	Samples
Normal bony	164
Amorphic	34
Abnormal	12

All samples were removed at operations. Among the clinical findings a considerable variation was noticed. In most cases, the samples consisted of the thickened anterior part of the stapedial footplate. The samples included even cases in which a broad marginal thickening was noticed as well as cases in which the whole footplate consisted of a thick, white bone with a rough surface. The comparison between the crystallic structure and the clinical findings gives no clear idea of the significance of the macroscopic appearance to the crystallic structure. Different shapes of the stapedial footplate appeared in all groups of the crystallic structure, but it seems that in the groups of abnormal crystallic structure there appeared more totally thickened footplates than in the normal crystallic structure group. This fact, however, has not yet been statistically proved.

As the samples in most cases were of a rather small size they could not

This study was supported by grants from the Sigrid Jusélius Foundation.

The World's Columbian Exposition of 1893

A notable event in the history of Chicago's development centered around the World's Columbian Exposition planned in 1892 to commemorate the 400th Anniversary *of the discovery of America Daniel H Burnham Chicago architect was* in charge of the planning enlisting the help of the most famous architects, sculptors and landscape designers of the country The plan transformed Jackson Park and the Midway later to become the site of The University of Chicago, from a swamp to a fairyland

The exposition attracted 27 1/2 million people in the six months that it was open—almost half the number of people living in the United States. It displayed the beauties of classic architecture starting a trend that was to last for a generation

A unique attraction was the giant "Ferris wheel built by Ferris to provide a view of the panorama from a maximum height of 250 feet

The Art Palace was preserved completely rebuilt in stone and is now the Museum of Science and Industry The Midway has become the home of The University of Chicago

The Chicago Plan

The plan developed by Burnham and his associates for the Columbian Exposition was expanded in succeeding years and was published by the Commercial Club of Chicago in 1909 as "The Chicago Plan This comprehensive plan took in all of Chicago and the surrounding country for a radius of about 60 miles. The preservation of the lake front including Jackson Park Grant Park the Museums, Lincoln Park the forest preserves and many smaller parks were all a part of this plan

Chicago has grown rapidly and now has a population of over 6 500 000 people in the metropolitan area It seems almost incredible that only 130 years ago it received its charter as a city with only a few thousand inhabitants It is only 140 years since some of the countryside that you will drive through this week was still the land of the Potowatomies, the Fox the Sauks and other Indian tribes

ACKNOWLEDGMENT

The author is indebted to the Chicago Historical Society for illustration and much information concerning the early history of the Chicago region



Fig. 2. Microradiogram of an otosclerotic footplate with morphic cry t llographic struc- t re Low mineralization Diffuse text re

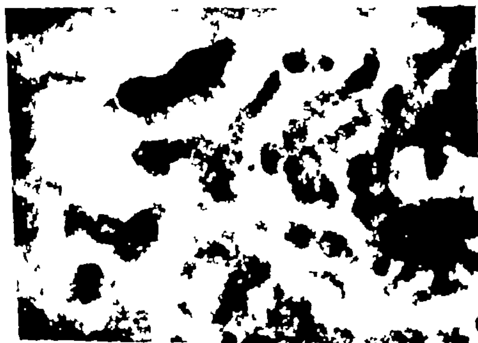


Fig. 3. Microradiogr m of otosclerotic footplat with bnormal crystallographic struc ture Cle mineralization Very high eral ization. Some osteocytes



FIG 1 Microradiogram of an otosclerotic footplate with normal crystallographic structure High mineralization

be histologically examined However the same samples could be used for a microradiographic examination This work is still continuing

Up to the present time, 40 samples have been microradiographically examined Of these, the crystallographic examination showed normal crystallic structure in 34 cases, in 3 cases the structure was amorphous and in 3 cases it was pathological The soft ray microradiography technique was used The bone pieces were embedded into metylacrylate and then cut into slices of 50–100 μ For the microradiographical examination 20 kV were used the film being Kodak Maximum Resolution Plates

In spite of the limited extension of the material it is already possible to make some observations at the present stage In the samples with normal crystallic structure, a clear mineral content could be observed The grade of this, as well as of the osteocytes, varied very much In the amorphous group the mineral content was obviously less than in the other groups. For this reason no microradiographic patterns could be obtained of part of the samples

In the group showing a pathologic crystallic structure, the mineral content varied highly as well as in the normal groups

In the following some microradiographic pictures will be presented (Figs 1 2 and 3)

The results at the present moment are showing a correspondence between the crystallographic findings and the microradiographic pictures

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ARE THERE COCHLEAR SHUNTS IN PAGET'S AND RECKLINGHAUSEN'S DISEASE?

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In 14 petrous bones from 14 cases of Paget's osteitis deformans and Recklinghausen osteitis fibrosa, foci of diseased bone replace the endosteal layer of the bony otic capsule The petrous bones demonstrate changes in the stria vascularis in the form of circumscribed swelling and flat thickenings, as described by M Kornfeld In contrast to the strial bods in otosclerosis, the strial changes in osteitis deformans and osteitis fibrosa also occur in areas where the normal endosteal layer still remain intact. There is no evidence of shunts in the spiral ligament of any of these temporal bones to cause the changes in the stria Also, no new lamellar bone deposits could be seen at the attachment of the spiral ligament On the other hand, in 8 petrous bones with Paget's and Recklinghausen disease there are several slender shunts in the basal turn of the cochlea, connecting the capillaries of the diseased bone with the spiral veins. In these cases, however in only one case are there signs of venous congestion in the inner ear In 13 petrous bones with osteitis deformans and osteitis fibrosa large shunts are seen in the internal auditory meatus between the vessels of the diseased bone lining the meatus and the internal auditory vessels within the canal. A marked thickening of the endosteal connective tissue provides evidence of venous congestion in the internal auditory meatus, due to the shunts. These shunts, causing a circulatory disturbance in the internal auditory meatus, may be responsible for the sensorineural deafness in Paget's and Recklinghausen's disease

The striking similarity of the histological picture in otosclerosis and in Paget's osteitis deformans was first observed by Otto Mayer in 1913 Since then various authors have confirmed that otosclerosis, Paget's disease and Recklinghausen's osteitis fibrosa have many histological features in common Nager & Meyer (1932) have concluded that the rigid and rather poorly reactive bony tissue may respond in the same way to a number of different disease processes. First, a new osteoplastic bone marrow is laid down. The old bone then undergoes osteoclastic destruction to be replaced by a network of unripe bone poorly supplied with fibrils, which is later remodelled into lamellar bone In Paget disease the bone shows a tremendous increase in the number and diameter of the small blood vessels.

The samples with a lack of or an obscure crystallic structure either had an obviously lower mineral content than those of the other groups, or even none

In this way these microradiographic measurements are confirming our previous presumption that the amorphous samples refer to otosclerotic foci, from which the normal bone structure has disappeared and the new ossification is starting The problem of the pathologic crystallic structure is, nevertheless, still unsolved

RÉSUMÉ

Une analyse est présentée de plus de 200 échantillons osseux De plus, les *différentes formes de cristaux constatées sont comparées avec les résultats* obtenus par la méthode microradiographique

ZUSAMMENFASSUNG

Eine Analyse von mehr als 200 Knochenproben wird dargelegt Ausserdem werden verschiedenartige Formen der Kristallstruktur mit den durch mikroradiologische Methoden gezeigten Ergebnissen verglichen

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Otol ryngological Clini Uni ersity f Turku Turku Finland

DISCUSSION

G E Shambaugh The etiology of the common and mysterious condition known as otosclerosis continues to elude us Mr Meurman states that his studies have not solved the mystery However we must keep in mind that we are dealing not with a *sclerosis* but rather an *osteoporosis* The lesion occurs in the dense endochondral bone of the labyrinthine capsule Everywhere else in the skeleton bone undergoes constant remodelling Only in the endochondral bone of the labyrinthine capsule does the adult possess bone completely inert and free from remodelling actively once it was laid down in foetal life It is in this inert bone that the otosclerotic lesion arises as a focus of new bone with very active remodelling It is to convert this actively enlarging focus to dense bone more like that of the normal endochondral capsule that Mr Petrovic and I have been conducting the studies that he will report on Thursday Let us remember whenever we speak of "otosclerosis" that we are actually talking about the exact opposite—a localized *osteoporosis* of the labyrinthine capsule

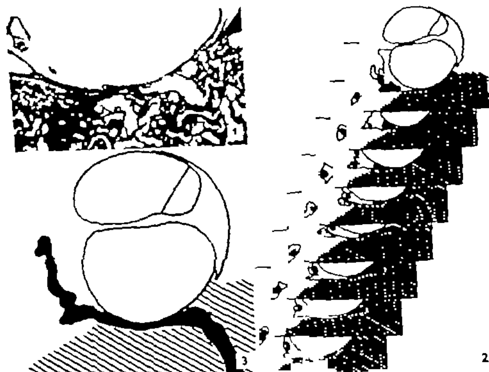


Fig. 1. Male patie t, 23 years old. Vertical secti through the basal turn f the left temporal bone show ng large deposit of otosclerosis, borde i g the scala tympani Shunt bet een otosclerotic essel and inferior piral in.

Fig. 2. Same case Fig. 1. Reconstruction f the course of the essel level plane

Fig. 3. Same case as Fig. 1. Reconstructed shunt between the focu f otosclerosi and the greatl dilated pi al ns.

hornfeld mad a histological study of 7 temporal bones with Paget s osteitis def rmans with the following results

In 2 temporal bones the process was mainly restricted to the periosteal layer The endosteal layer was intact. Th stria vascularis was found to be normal in these temporal bones. In a second group of 5 temporal bones all layers of the labyrinthine capsul were severely affected and the abnormal bone had reached the cochlear endosteum at many points. In all bones of this group th stria showed abnormalities. Most commonly a circumscribed swelling either in the form of a flat thickening or of a pedunculated nodule were found, both consisting of small blood vessels and strial epithelium K rnf ld tried *without* success to find shunts between the blood vessels of the I aget bone and the blood vessels of the inner ear similar to the shunts we ha e found in otosclerosis.

In connection with k rnfeld's work we have examined our own specimens f Paget disease (12 cases, 17 petrous bones) and Recklinghausen s o teitis fibrosa (2 cases, 4 petrous bones)

The exuberant vascularity of an actively growing focus of otosclerosis has been repeatedly described by otohistologists. Every deposit of otosclerosis develops its own more or less independent vascular system which arises in several places from the arterial capillaries of the normal otic capsule and drains back again into the venous capillaries. Anson & Bast (1949) have shown that there is normally *no* vascular connection between the vessels of the bony otic capsule and the blood supply of the membranous labyrinth

In 1964 we observed changes in the stria vascularis in relation to foci of otosclerosis growing through the endosteum of the otic capsule and bordering directly against the spiral ligament These changes in the stria consisted of a circumscribed increase of vascular loops and a proliferation of the strial epithelium So-called shunts, or pathological vascular connections, were seen between the vascular spaces of the otosclerotic focus adjoining the ligament and the spiral capillaries running through the ligament itself Further shunts were also demonstrated in the basal turn of the cochlea between otosclerotic vessels and the spiral veins of the inner ear These shunts cause venous congestion of the inner ear pending the gradual *enlargement by osteoclasts of the normally narrow bony canals transmitting* the veins across the otic capsule As long as the venous congestion persists increasing damage to the inner ear may result It is probable that the sensorineural deafness in otosclerosis is due to the shunts causing venous congestion of the cochlea. Following a suggestion by Mr Anson several shunts were reconstructed from otosclerotic ears by my collaborator Jurg Mann One example was demonstrated at the Workshop in 1967 Here we have a second example

In a patient, 25 years of age the vertical section through the basal turn of the left temporal bone (Fig 1) shows a large shunt between the vessels of an otosclerotic focus in the basal turn and the inferior spiral vein Reconstruction of the course of these vessels on a level plane (Fig 2) shows a wide shunt arising from the focus of otosclerosis and draining into the grossly dilated spiral vein and the equally dilated vein of the cochlear aqueduct (Fig 3)

Following up our histological findings, Kornfeld (1967) correctly made the demand

> Since there is a considerable histological similarity between otosclerosis and Paget s disease it would seem reasonable to assume that inner ear changes in Paget s disease would resemble those in otosclerosis if the underlying osteodystrophy affects the same portions of the labyrinthine capsule If shunts between the capsular and cochlear circulation in otosclerosis are as frequent as claimed by Rüedi it is to be expected that they would be at least equally frequent in Paget s disease because in the latter there is evidence for the presence of multiple arteriovenous communications in various diseased bones of the body

completely replaced by diseased bone in several places. Pathological changes in the stria vascularis were seen in this group only involving 9 petrous bones and consisting of circumscribed or diffuse thickenings, atrophy and cysts, as noted by Kornfeld. The structure, but not the localization, of the circumscribed thickening resemble the strial changes seen in otosclerosis. The swellings of the stria in otosclerosis are confined to the area where the otosclerotic bone comes into direct contact with the spiral ligament. In osteitis deformans or fibrosa, however, similar strial changes are also seen in the region where the endosteum bordering on the spiral ligament is still intact. Histological evidence offers no explanation for the strial changes in osteitis deformans or fibrosa. Kornfeld's findings are confirmed in that there is no evidence of shunts in the region of the spiral ligament and no other signs of venous congestion. In particular, no new deposits of lamellar bone could be demonstrated.

On the other hand, we have found undoubted evidence of shunts between the vessels of the inner ear and the vessels in the diseased bone in 8 petrous bones with Paget's and with Recklinghausen's disease. These shunts were situated in the basal turn of the cochlea which is also the favourite site for shunts in otosclerosis.

A 70-year-old patient with Paget's disease (Case No. 2) shows a deposit of diseased bone penetrating the endosteum of the left basal turn of the cochlea, seen here in horizontal section. There is a *slender* shunt (Fig. 5) between the fine vessels of the osteitis deformans and the inferior spiral vein. This shunt has been demonstrated already at the 3rd Workshop in Chicago.

A larger shunt is present in a 3-year-old case of Paget's disease (No. 1) between the vessels of the bone and the inferior spiral vein, again in the basal turn of the cochlea (Fig. 6) near the origin of the calcified aquaeductus cochleae.

Finally another convincing shunt appears, again in the basal turn of the cochlea (Fig. 7) in a 54 year-old case (No. 14). The opened marrow spaces of the modiolus, which is still surrounded by normal bone, show newly formed pinkish osteoid tissue which is being laid down as a result of congestion. The deeper layers of this same temporal bone reveal further evidence of increased circulatory activity in the markedly dilated inferior spiral vein. Apart from this last example the few slender shunts present in the basal turn of the cochlea in the remaining temporal bones have not given rise to any congestion of the spiral vessels.

Since we have discovered an arterial shunt in the internal auditory meatus from a case of otosclerosis, we have also made a careful search of this area in the cases of Paget's and Recklinghausen's disease.

In 16 petrous bones the diseased bone replaces the normally dense endosteal layer of the internal auditory meatus. In spite of this filling in with pathological bone the lumen of the internal auditory meatus is only slightly reduced in one case (No. 3). In the remaining cases the bony



FIG. 4 54-year-old case of Paget's disease (No. 14)

After Kornfeld's excellent description of the pathological changes in the bone structure of the petrous bones any repetition would be superfluous. In spite of the many points of similarity between the histological pictures of the temporal bone in Paget's and Recklinghausen's disease they are generally quite easy to distinguish from otosclerosis. It is well known that the changes in the bone structure in otosclerosis are confined to the human bony otic capsule. To begin with foci are laid down in the enchondral layer and extend from there to involve both the endosteal and the periosteal layers. In contrast Paget's and Recklinghausen's disease both affect different bones and the entire bony skull. Having involved the base of the skull the disease may advance to attack the petrous bone on a broad front. In a 54-year-old case of Paget's disease (No. 14) the diseased bone surrounds the hard bony otic capsule (Fig. 4). The periosteal layer has first been attacked, then the enchondral layer and finally the endosteal layer has been replaced with diseased bone. As a result of the changed static condition in the region of the base of the skull and the petrous bone spontaneous fractures commonly occur in the otic capsule.

Our histological findings in the bony otic capsule and the pathological changes in the neuroepithelial elements of the inner ear are summarized in Table 1. We will only comment on the condition of the stria vascularis and the demonstration of shunts between the vessels of the inner ear and those from the bone in osteitis deformans or fibrosa.

In 14 petrous bones the endosteal layer of the bony capsule has been

Organ of Corti	Ganglioncells	Bony cochlea	Meatus acusticus internus
Small layer of indiff. cells	Reduced in basal turn. Hemosiderin	*Shunt.* Fractures	Surrounded with pathologic bone. Big *shunts*
Small layer of indiff. cells	Reduced in basal turn	*Shunt.* Fractures	Surrounded. *Shunts*
Normal	Reduced i basal turn	*Shunt.* Fractures	Surrounded. Big *shunts*
Postmortal disintegration	Normal		Surrounded and somewhat narrowed. *Shunts*
Postmortal disintegration	Normal		Surrounded. *Shunts*
Normal	Normal		Surrounded. *Shunts*
Postmortal disintegration	Normal		Surrounded
Postmortal disintegration	Normal	*Shunt*	Surrounded. Big *shunts*
Normal	Reduced in beginnig of basal turn		Surrounded. Big *shunts*
Postmortal disintegration	Normal		Normal
Absent in all turns	Reduced in all turns		Surrounded. *Shunts* secondary reclosed
Absent in all turns	Reduced in all turns		Surrounded. *Shunts* secondary reclosed
Postmortal disintegration	Normal		Surrounded. *Shunts*
Postmortal disintegration	Reduced in all turns		Normal
Postmortal disintegration	Reduced in all turns		Normal
Normal	Normal		Normal
Normal	Normal	*Shunt*	Surrounded. *Shunts*
Normal	Normal		Normal
Normal	Normal	*Shunt.* Fractures	Surrounded. Big *shunts*
Absent in basal turn	Reduced in basal turn		Surrounded. Big *shunts*
Postmortal disintegration	Reduced in basal turn		Surrounded. *Shunt*

TABLE 1

Name	Age	Hearing	Diagnosis	Endost	Stria vascularis
1 T B	73 y	For 3 yrs. has had slight diminution of hearing	Paget	R Replaced by patholog. bone L. Replaced	Narrow Few hyaline blood vessels independent of path bone Narrow Few hyaline blood vessels independent of path. bone
2. H R.	79 y	?	Paget	R. L. Replaced	 Normal
3 K P	69 y	?	Paget	R. Replaced L.	Postmortal disintegration
4 St B	80 y	?	Paget	R. Intact L. Replaced	Normal Cysts. Enlarged vessels. Circumscribed atrophy independ. of patholog. bone
5 R. A	71 y	?	Paget	R Int ct L. Replaced	Normal Normal
6 M	79 y	?	Paget	R Replaced L.	Narrow Localized atrophy
7 B A.	50 y	?	Paget	R. Intact L.	Normal
8 H L.	75 y	?	Paget	R. Replaced L. Replaced	Narrow Indifferentiated laye in all turns Narrow Indifferentiated layer in all t rns
9 G	36 y	?	Paget	R. Intact L.	Postmortal disintegration
10 Ch T	56 y	?	Ostitis fib osa Recklinghausen	R. Intact L. I t ct	Postmortal disi tegration Postmortal disintegration
11 B U	77 y	Deaf	Ostitis fibrosa Recklinghausen	R. Replaced L. Replaced	Circumscribed thickenings independent f pathologic bone Circumscribed thi kenings i dependent of pathologic bon
12 B. H	90 y		Paget	R. Intact L.	Normal
13 H. G	78 y	Deaf Conversation possible without difficulty	Paget	R. Replaced L. Replaced	Normal Normal
14 6	54 y	?	Paget	R. R placed L.	Cysts. Postmort l disi tegrati



Fig. 7 84-yrs -old case f Paget's disease (N 14) Sh nt between the essel f the Paget-bone and the essel f the modiolus.

Fig. 8. 78-year-old case of Paget' disease (No. 13) Numerous hu ts between the ins of the Paget-bone and the internal auditory ins.

shunts between the veins in Paget s bone and the widely dilated internal uditory veins (Fig. 8) The endosteal connective tissue becomes greatly thickened as a result of this chronic venous congestion.

The fact that these large shunts between the essels in the d seased bone nd the cochlear vessels within the internal auditory meatus are very com mon in Paget disease raises the question whether the blood circulation in the modiolus may be disturbed by a peripheral extension of this congestive proces

One may further question whether changes in the ganglion cells may arise and possibly also whether changes in the perilymph may occur as they do in acoustic tumours Our histological material does not pro ide the an wers to these questions. There are no details concerning the hearing n our cases. The histologically established changes in the neuroepithelial lement f the cochlea could be accounted for by the age of our 60- to 80-year-old cases. Lindsay & *Perlman* (1936) have reported 4 patients with ostc ti deformans with hearing impairment All showed some sensori neural los in all frequ ncies with a more severe los in the high frequencies. Also Sparrow & Du all, III (1967) described 5 further cases of Pag t disease with hearing impairment Apart from 2 cases with conduct e deafnes all cases sh wed a sensorineural hearing loss. In contrast with se s rineural deafness in tosclerosis the hearing los in all these cases nly began when the disease wa well advanced Again, in contrast with t sclerosis, Sparrow & Duvall's cases lso howed a sensorineural loss in ll frequen ies. Further udiological tests, especially peech discrimination udiometry should h lp to solve the question whether the sensorineural deafness n osteiti deforman or fibrosa could be caused by venou congestion within the internal audit ry meatu resulting from shunts in this region





Fig. 5 79-yea -old ca with Pag t dise se (N 2) Sl de hu t between th essel of th osteitl d f rm ns and th i feri piral v in

Fig 6. 73-y -old ca f P g t dise se (No 1) Larg h t between th ves l f th P get bon nd the i feri piral in.

meatus is of normal width Moreover in 15 temporal bones we have found large shunts between the vessels of Paget s bone and the internal auditory vessels, running alongside the nerve within the canal These shunts are in our view of some importance for the spatial relations within the internal meatus.

In the 78 year-old case of Paget s disease (No 13) there are numerous

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DISCUSSION

C Kelemen After mentioning examples of shunt in Paget of the temporal bon the fact is described that the wall of the facial canal l formed frequently to a large e tent by otosclerotic bone without dam ge to the facial function It is difficult to imagine that the same substance shunted into th cochlea should damage the cochlear end-organ leaving the f cial intact.

J R Lindsay I wish to show some slides from n elderly case of Paget s disease associated with profound bilateral deafness. These slides confirm the bserv tion of multiple "shunts described by Mr Rüedi They illustrat lso a second f ct r the presence of fractures through th bony capsul at the region of the round window and the posterior canal ampulla. These are associated with a h perplastic reaction l the perilymphatic spaces consisting of extensive f brosis. The fibrosi i related to the areas where the defect in the bone in lves the ner bo y layer

The question which l raised and as y t un nswered by the hi topathology t the present stage f ou information is how to interpret the relation f the lesion to the disturbance of function. I the disturbance in circulation the predisposi g factor or is the existence of an irritativ eaction caused by the foci the more important factor?

W House Injection techni on th temporal bone ha hown that th i ternal uditory artery supplies more than just the inner ear If this i true do you feel enou congestion f stria ascularl i more l k ly?

C Shambaugh Mr Rüedi has, f th first time given us a logical explan tion for the sensori-neural loss that occurs in the majority of cases of stapedial otosclerosis, nd in pure cochlea otosclerosis. I have been impressed by the tendency of the sensori-neural loss to progress for time and then to stabilize n t least some cases. If th sensori-neural los i due to nutritional or oxygen depri tion of the hai cells produced by a shunt does thi mean that shunt ca sh ivel-up or disappea fter tim ?

L. Rüedi (Reply) to Mr *Kelem n* You put the question what stra ge material rculating through the shunts in otosclerosi ? First, we have t define the expres ion shunt "Shunt mean histologically visible connection between arterial or enou blood vessels. Therefore within the lumen of a shunt blood i irculati g

RÉSUMÉ

Dans 14 rochers de 14 cas d'ostitis deformans Paget et d'ostitis fibrosa Recklinghausen la partie endostale de la capsule labyrinthique est remplacée par l'os pathologique. Dans ces rochers la stria vascularis présente les altérations décrites par M. Kornfeld sous forme d'enflures localisées et d'épaississements allongés. Il n'y a pas des shunts dans le ligamentum spirale qui pourraient être la cause de ces altérations. Dans 8 cas de maladie de Paget et Recklinghausen on trouve par contre dans la spire basale quelques petits shunts reliants les capillaires de l'os pathologique aux veines spirales. Seulement dans 1 cas il y a des signes de congestion veineuse. 15 rochers présentent des grands shunts au niveau du méat acoustique interne entre des vaisseaux sanguins de l'os pathologique de la paroi et des vaisseaux labyrinthiques dans le méat. Un élargissement endostal suggère l'existence d'une congestion vasculaire. Il est possible que la surdité de perception dans les cas d'ostitis deformans et d'ostitis fibrosa soit causée par des troubles circulatoire due aux shunts dans le méat acoustique intern.

ZUSAMMENFASSUNG

In 14 Felsenbeinen von 14 Fällen mit Ostitis deformans Paget und Ostitis fibrosa Recklinghausen ersetzt der kranke Knochen stellenweise die endostale Schicht der knöchernen Schnecken Kapsel. In diesen Felsenbeinen sind die von M. Kornfeld beschriebenen Veränderungen der Stria vascularis vorhanden in Form von umschriebenen Anschwellungen und leistenförmigen Verdickungen. Im Ligamentum spirale dieser Felsenbeine können keine Shunts als Ursache der Striaveränderungen nachgewiesen werden. Hingegen finden sich in 8 Felsenbeinen mit Ostitis deformans und Ostitis fibrosa ebenfalls in der basalen Schneckenwindung einige zarte Shunts, welche die Kapillaren des kranken Knochens mit den Venae spirales verbinden. Anzeichen einer venösen Innenohrstauung sind nur in 1 Fall vorhanden. Ausserdem sind in 15 Felsenbeinen mit Ostitis deformans und Ostitis fibrosa im Meatus acusticus internus grosse Shunts zwischen den Gefässen des kranken, den Meatus begrenzenden Knochens und den im Meatus verlaufenden Innenohrgefässen vorhanden. Für eine shuntbedingte Abflussstauung im Meatus acusticus internus spricht eine Verbreiterung des bindegewebigen Endostes. Möglicherweise entsteht die Perzeptionsschwerhörigkeit der Ostitis deformans und der Ostitis fibrosa infolge einer shuntbedingten Zirkulationsstörung im Meatus acusticus internus.

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DOMINANT HEREDITARY CONDUCTIVE DEAFNESS THROUGH LACK OF INCUS-STAPES JUNCTION

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This report concerns an extensive family research in which a regular dominant conductive deafness can be traced in four generations. The middle-ear operation of four ears on three symptom-carriers showed a missing connection of the incudo-stapedial joint.

Reference is made to the fundamental research work of Anson, Bast and collaborators, regarding the differentiated evolution of the middle ear ossicles and the incudo-stapedial junction. In this small malformation of the middle-ear ossicles it must be assumed that in affected members a dominant genetic factor prevents in the sixth to the seventh fetal week the rotation and the joint of the distal end of the incus with the blastema of the stapes, the result is an inborn conductive deafness.

In cases of conductive deafness with a normal ear-drum, normal pneumatization and no symptoms of inflammation, we diagnose generally an otosclerosis. During the operation we sometimes discover another cause such as congenital fixation of the stapes or aseptic necrosis of the incus-stapes junction. At the Detroit Symposium of Otosclerosis I mentioned a family tree with otosclerosis over three generations and congenital stapes fixation in the fourth generation, with the interpretation that the same hereditary factor may lead to otosclerosis or congenital stapes fixation.

Today I deal with another familiar ear deformity. It is to the credit of Ombredanne (1960, 1960, 1962, 1964) that he elaborated the conception of small malformations in the middle ear. One of the predominant areas of malformation is the incus-stapes joint, as is confirmed by Hough (1958, 1959, 1963), Kelly (1963), Tolan & Wilson (1958), Henner (1960) and Soos (1960). Morphological variation at this place are not so seldom. But already before 1946 Anson & Bast (1946) mentioned that one should be extremely critical in the interpretation of these variations as pathological facts. Because of the maturation of the ossicles attained during the fetal period, and the profound change of the origin elements prior to the definite construction of the ossicle-chain, variations may occur occasionally. Only the missing junction of the incus-stapes joint is pathologic.

It is an honour for me to express my admiration for and homage to the scientific work of Anson & Bast (1946) and co-workers. All our know-

to Mr *Lindsay* After demonstrating a case of Paget s disease you asked if the productive labyrinthitis is produced by some chemical agent or due to a large fracture or as in otosclerosis due to venous stasis? In our cases of otosclerosis with productive labyrinthitis lamellar bone formation probably caused by venous congestion was always present As far as I could see there is no lamellar bone formation present in the Paget s case and there are no other signs of venous congestion The cause of the productive labyrinthitis is unknown to me

to Mr W *House* The endosteal layer of the bony otic capsula is histologically a closed barrier Biochemically this barrier may be insufficient But only after the formation of shunts can a great quantity of venous blood flow into the soft tissues of the inner ear producing here a stasis until the channels in the bony otic capsula are dilated

to Mr *Shambaugh* A shunt once developed may close again when the otosclerotic focus becomes inactive and lamellar is filling up the narrow spaces. Other shunts may stay open but the damage to the inner ear stops as soon as the bony channels leading the blood vessels from the membranous labyrinth to the venous sinuses are sufficiently enlarged to overcome the blood stasis within the inner ear spaces.

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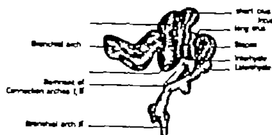


Fig 1

Fig 2

Fig 1 Primitive joint between Reichert cartilag to th bla t ma of the incu body Fifth f t l w ek (Anson & Bast Strickland nd co-w rk rs)

Fig 2 Secondary reunion between the long crus of th incus t the stapes. Sixth to the seventh fetal week.

ledge and the modern embryologic conception of the visceral descendance of the middle ear is based on the imposing investigations of these authors. Thus the malleus and incus are not totally descending from the first visceral arch, but only the head and the neck of the malleus and the body of the incus The manubrium of the malleus and the long crus of the incus belong to the second arch There is a first primitive joint—a bridge—between Reichert s cartilage to the blastema of the incus body in the fifth fetal week This joint dissolves and, during the sixth to the seventh fetal week, a secondary reunion arises between the long crus of the incus to the stapes This astonishing development and the attraction of the two bony surfaces of the small ossicles, end in a back differentiation in a mesenchym tissue, from which, in the 23rd week only the cartilage and definitive incus stapes joint is created This highly differentiated mechanism progresses with incredible precision Variations are not so seldom, but the missing joint is a rarity Genetic factors are mentioned, but genealogic investigations are unknown Hanhart (1949) describes family trees with higher deformities, such as atresia auris associated with palatoschisis

Description of a family with juvenile conductive deafness caused by lack of joint between incus and stapes

The first observation concerns a man born in 1932 (1204 62) with bilateral conductive deafness, normal ear-drums and normal pneumatization Under the diagnosis otosclerosis or congenital stapes-fixation, we performed a middle ear revision on the left side but to our surprise we observed the following deformity

The long crus of the incus was curved like a hook the head of the stapes was lacking and there was no connection between the incus and

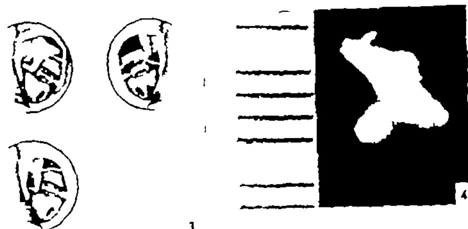


Fig. 2. Status f the three operated ears with missing con ection between incu nd stapes.

Fig. 4 Photograph f the incu with hook on the distal end.

the mobile stapes. A new junction from the stapes to the malleus gave a good functional result.

Some months later the right ear was operated on and its status was exactly the same

The shortened long crus of the incus was like a hook. Some small fibres of connective tissue to the reduced head of the stapes were present. The restored ossicle-chain gave an excellent functional result

The patient informed us that his two brothers have had a similar hearing loss since youth We had an opportunity to perform a middle ear revision n ne ear of one of his brothers.

K S. 525 63 Here too, the status was of the same kind stapes with small head, and curved distal end of the long crus of the incus with a fine band of connective fibres.

Th *hi tology* of two incus shows that no signs of inflammation exist. There is a normal structure f bony tissue with marrow canals and n rmal ascularization. From a marked and fine limited zone in the distal end—like a nest—connective fibres take their origin

On the basis of these hard-of hearing brothers, we started *genealogic* inve tigation and we established a complete family tree over five genera tion beginning in the early 19th century with 342 members. Except for f ur members, we h d information on hearing function in all cases. It is xtremely interesting that bilateral juvenile conducti e deafnes start with me member (30) in the sec nd generation. Only direct descendants from thi female proband are affected A healthy-born member never has a case of thi type f deafness in th next generation

In 12 cases ju enile deafness was found The li ing hard-of-hearing members of the generation III IV and V had a complete audi metric investigation

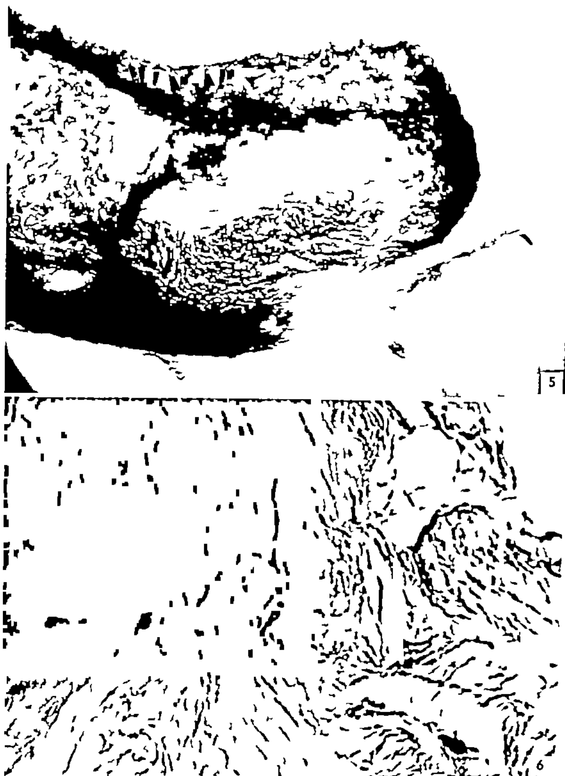


Fig. 5 Co ctl fibres, lik a n t, l th dist l d f the lneu

Fig 6 Fin limited bord l betw n ectl d Lo tissu \ ig f l fl mmati n

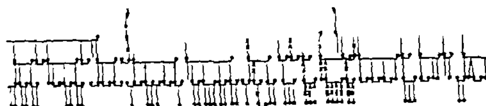


FIG. 7 M in part f th f mily tree ■ ● Juvenile conductiv deafness.

Furthermore, it may be of interest that all affected members, with one exception, have hypertrophic and thickened ear lobules. It is probable that this associated symptom is attached to the same dominant genetic factor in the sense of polyphony

Further ear revisions are planned, the next on a child of the fifth genera tion This operation was performed in Nov 198 The same status of lacking incus-stapes junction was found We hope t confirm in these cases our following conclusions

1 In each case of bilateral juvenile conductive deafness one of the par ents is a holder of the same syndrome A generation is never left out All holders of the gene are simultaneous holders of the syndrome There is complete penetrance and a regular dominance

2. The frequency of the gene holders in the descendance amounts to 50 %

3 The descendance f healthy members is, in each case, *free* from the syndrome The hereditary path in generations I and II cannot be judged In particular we do not know if the first member II/10 has already a h reditary deafness, or if it happened in this case to be a dominant muta tion



FIG. 8 Associated mpt m of ffected members hypertrophic nd thickend lobules.

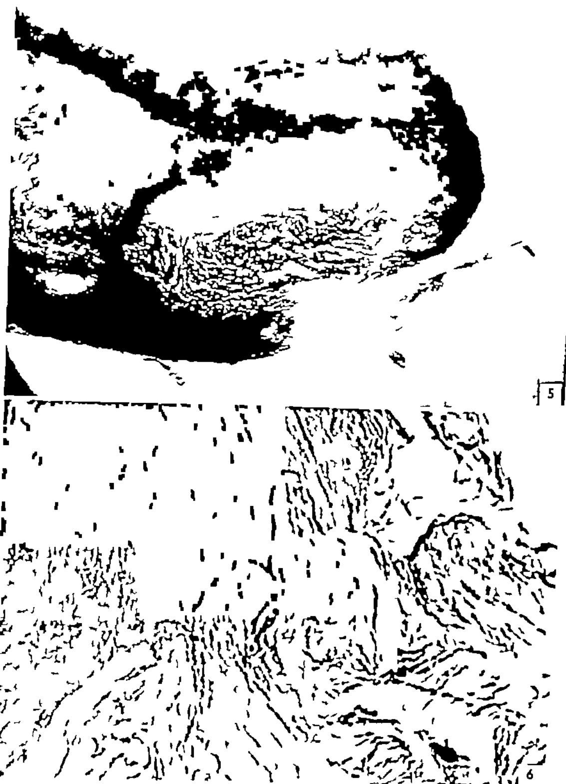


Fig 5 Con ect fibres l ke a nest, in the dist l d f the incus.

F 6 Fi e limited borderlin between co ecti d Lon tl su \ lg f l flammatio

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4 The syndrome is independent of sex.

5 We have to assume that in affected members a dominant genetic factor prevents in the sixth to the seventh fetal week the rotation and junction of the distal end of the incus with the blastema of the stapes, resulting in inborn conductive deafness

RÉSUMÉ

Rapport sur une investigation généalogique d une famille dans laquelle existe au cours de 4 générations une surdité de transmission congénitale bilatérale de dominance régulière La révision de 4 oreilles de trois porteurs du syndrome montre une jonction déficiante entre l enclume et l étrier Les travaux embryologiques du développement de l oreille moyenne de Anson Bast et collaborateurs permettent de comprendre le méchanisme differencié de la formation de l articulation incudostapédienne Pour nos probands il faut admettre un facteur génétique qui a empêché la rotation de la branche longue de l'enclume et l union avec l étrier entre la 6e et la 7 semaine fétale d ou résulte la surdité de transmission congénitale

ZUSAMMENFASSUNG

Es wird über eine ausgedehnte Familienuntersuchung berichtet in der eine regelmässig dominante Schalleitungsschwerhörigkeit in 4 Generationen nachgewiesen werden kann Die Mittelohrrevision bei 3 Merkmalsträgern an insgesamt 4 Ohren ergab einen fehlenden Schluss am Amboss-Steigbügelgelenk Es wird auf die grundlegenden Untersuchungen von Anson und Bast und ihren Mitarbeitern *hingewiesen welche die differenzierte Entwicklung der Gehörknöchelchen* und der Amboss-Steigbügelverbindung eingehend darlegen Es muss bei dieser Störung angenommen werden dass ein erblicher Faktor bei den Probanden eine Drehbewegung und Vereinigung des Ambosschenkels mit dem Steigbügelblastom in der 6 –7 Foetalwoche gestört hat so dass die congenitale Schalleitungsstörung entstand

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MOVEMENTS OF THE VOCAL CORDS

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and J H OGURA M.D

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Vocal cord movem nt induced by laryngeal erve stimulation was compared with that of respirati n, phonation and deglutition and the results f electri al stimulation f the external superior laryngeal and recurrent nerves and their branches in d gs at different frequencies a d voltages are described Th posterior cricoarytenoid muscle (abductor) has a low frequency haracteristic when compared with the adducto muscles. The frequency characteristics of the cricothyroid muscl (tensor) is between th bductor an l the adductor

Abduction and adduction of the vocal cord in the phases of respiration, phonation and deglutition appear to be simple Actually its neurophysiologic responses are not readily explained nor clearly understood Ana t mical and physiological correlation by means of electrical stimulation of the human uperi r laryngeal nerve was observed by Ogura & Lam in 1953

Nakamura *et al* (1959 1961 1963) observed that the use of low fre quency timulating currents on the recurrent laryngeal nerves caused the opening of the gl ttis while higher frequency currents closed the glottis, nd thi phen menon was also observed by Brewer & Dana (1963) and Ha t (1966) although no satisfactory explanation wa given These ex periment wer perf rmed to exp lore the mechanism of this phenomenon as well a add further inf rmation in regeneration of the recurrent laryn geal nerves in our larynx transplantation studies (Ogura *et al* 1966, 1967)

EXPERIMENTAL METHODS

The experiments were carried out on 6 dogs. In the supine position, anteri r pharyngot my exposure of the larynx was obtained using intravenou anesthesi with Sodium Pentobarbito. After removal of the hyoid bone the sternohy id and ternothyroid muscles were divided from their superior ttachment and then the nterior wall of the hypopharynx was opened to btain a direct view f the glotti

Electromyographic recording of th laryngeal muscles wa made by

Thi study w pported by NIH Grant N.B. 04200

DISCUSSION

P Livingstone The gap between stapes and deformed incus is not always due to a genetic cause The condition is more common in those cases where the cause is teratogenic and occurs in about 10% of cases How does fat get into the middle ear in these cases of *meatal* atresia?

F Sooy I have noticed that you have used polyethylene tubing in reconstructing these cases and would like to ask if you have found this to be a lasting technique and if not do you now use another method in the management of such cases?

F Escher (Reply) to Mr *Livingstone* The variety of middle ear malformations is very high The special and unknown situation in our family is the fact that the small malformation of lacking an incus-stapes joint is identical in different members and that this phenomenon has a dominant heredity

to Mr *Sooy* Plastic material for repair of the ossicle chain was used three years ago Now we prefer to employ the turned original incus for a columella effect

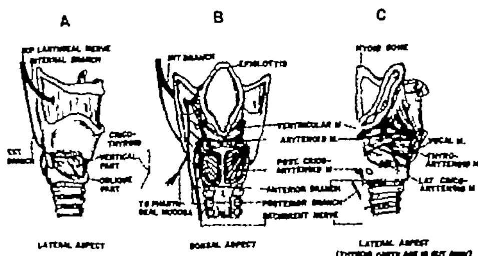


Fig. 1 Thi figure show muscolat re nd i nervation of the ca ine l rynx.

The external branch runs downward and forward on the external sur face of the inferior constrictor muscle and passes deep to the insertion of the sternothyroid muscle to supply the oblique and vertical part of the cricothyroid muscle as the motor nerve

2 *The recurrent nerve*

The recurrent nerve divides into two branches at the level of the 2nd trachea ring. The one branch, which is called the ramus posterior pro-

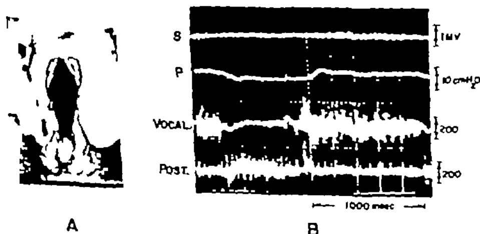


Fig. 2 (A show the lary geal iew the in piratory phase of relall respiration. Both oc l ord re l lightly lateral from the l termediat line Clottal opening is 6 mm wide (B) he relation hip l the subglottic press re chang nd the action pot ntial pattern of the l ryngeal muscles S Sound P bglottic pressure; Vocal EMG of the oc l muscle; Post EMG of the posterior cricoaryten id muscle

inserting a bipolar concentric needle electrode and subglottic pressures were measured by inserting a trocar into the trachea and attached to the cathode ray oscillograph via a strain gage type transducer

In order to compare vocal cord movement at a time of respiration phonation and deglutition with that induced by electrical stimulation of the laryngeal nerves, the experiments were first performed under normal innervated state and three observations were made in respiration phonation, and deglutition

For the nerve stimulation experiments of the superior and recurrent laryngeal nerves, the trachea was sectioned at the level of the 3rd ring to prevent passive movement of the vocal cords by respiratory air current The internal branch of the superior laryngeal nerve was bilaterally sectioned at its entrance into the thyroid membrane and the external branch of the superior laryngeal nerves and the recurrent nerves were carefully isolated and divided approximately 5 cm away from their entrance into the larynx. Since the inferior constrictor muscle has some effect on vocal cord movement (Arnold 1961 Hiroto 1966 Levit *et al* 1965) the nerve branches distributed to the inferior constrictor muscles were transected

In the first part of the stimulation experiments, peripheral stumps of the external branch of the superior laryngeal nerves and the recurrent nerves were electrically stimulated

In the second part of the stimulation experiments, the single nerve branch to each individual muscle was stimulated The external branch of the superior laryngeal nerve and the recurrent nerve were pursued to their peripheral fibers and divided at their diverging portions of the nerve branches distributed to each intrinsic laryngeal muscle and electrical stimulation was applied to each nerve branch individually or simultaneously

The stimulus was produced by a stimulator with coupled stimulus isolation unit (Grass Instrument Co) delivered to nerves by bipolar shielded silver wire electrodes at 3 mm polar distance Stimulus voltage ranged 0 1 to 10 volts (threshold voltage was 0.3 volts in average) and stimulus frequency varied from 1/sec to 100/sec with square wave pulses of 0 1 millisecond duration

RESULTS

A *Innervation of the Larynx*

1 *The superior laryngeal nerve (Fig 1)*

The superior laryngeal nerve divides into an internal and an external branch The internal branch subdivides into two branches immediately after entering through the thyrohyoid membrane one branch is distributed to the epiglottis and the other descends to make the anastomosis with the posterior ramus of the recurrent nerve in addition to its laryngeal and pharyngeal distribution as the sensory nerve

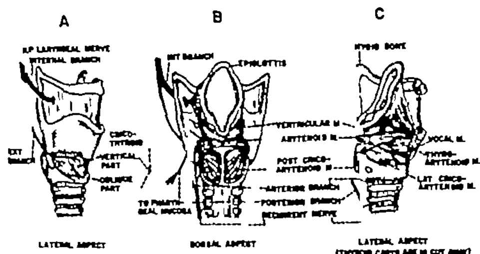


Fig. 1 This figure shows neural structure and innervation of the canine larynx.

The external branch runs downward and forward on the external surface of the inferior constrictor muscle and passes deep to the insertion of the sternothyroid muscle to supply the oblique and vertical part of the cricothyroid muscle as the motor nerve.

2. *The recurrent nerve*

The recurrent nerve divides into two branches at the level of the 2nd trachea ring. The one branch, which is called the ramus posterior pro-

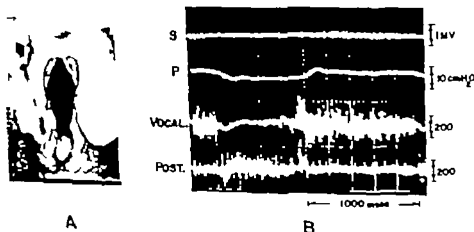


Fig. 2 (A) shows the laryngeal view in the inspiratory phase of relative respiration. Both vocal cords are in slightly lateral from the intermediate line. Glottal opening is 6 mm wide. (B) shows relationship of the subglottic pressure change and the action potential pattern of the laryngeal muscles. *S* Sound; *P* subglottic pressure; *Vocal* EMG of the vocal muscle; *Post* EMG of the posterior cricoarytenoid muscle.

gresses in a posterior lateral direction and connects with the internal branch of the superior laryngeal nerve. The other called the ramus anterior proceeds in an anterior internal direction and divides into the nerve branches to the posterior cricoarytenoid muscle, the arytenoid and ventri cularis muscle, the lateral cricoarytenoid muscle and the thyroarytenoid muscle (external thyroarytenoid and vocal muscle)

B Normal Vocal Cord Movement during Respiration Phonation and Deglutition

1 *Respiration (Fig 2)*

Both vocal cords are in the intermediate position during quiet respira tion however the glottis becomes slightly wider during inspiration (Fig 2 A) and slightly narrower during expiration Electromyogram shows that the abducting posterior cricoarytenoid muscle is more active during inspira tion decreasing the subglottic pressure, while the adductors increase their activities with each expiratory cycle The electrical discharge of the muscle starts to fire before onset of each respiration (Fig 2 B)

2 *Phonation (Fig 3)*

Fig 3 A illustrates a position of the vocal cords at a time of phonation (whine) both vocal cords take the median and elongated position Electromyogram showed considerable discharges in the adductor muscles and the cricothyroid muscle as compared with activity at the time of respiration There are time delays between the onset of the muscle action potential the starting point of intratracheal pressure development and the initial sound at the beginning of phonation The cricothyroid muscle begins activity earlier than that of the adductors (Fig 3 B)

3 *Deglutition (Fig 4)*

The closure of the glottis begins with the anterior portion and proceeds posteriorly and the arytenoid cartilages are tightly pressed against the epi glottis (Fig 4 A) and finally sphincteric closure of the glottis results The adductor muscles show marked activity during glottic closure phase corre- sponding to negative value of the subglottic pressure and activity of the cricothyroid muscle ceases at this time and reappears during glottal open ing phase of deglutition (Fig 4 B)

C. Vocal Cord Movement Induced by Electrical Stimulation of the Laryngeal Nerves

I *Control position*

Fig 5 A shows the position of the vocal cords when all of the laryngeal nerves were cut All of the intrinsic laryngeal muscle became atonic and

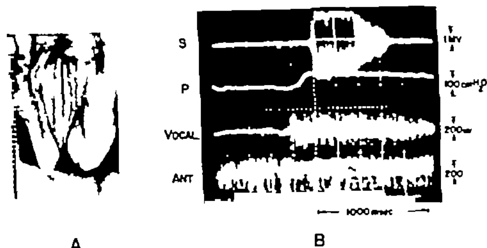


Fig. 3. (A) show the laryngeal few t time f pho tion (whl) Both ocal cord take the median position nd leng te bout 8 mm more compared with respiration. Scal mm. (B) show the rel tionsh p bet een the d bl tone the subglottic pressure hange d the action potential pattern of the lary ge l muscles w th phonatio (hine) Action potential of the ocal muscl t rt 200 msec ea ller tha the begi ing of the ddibl tone nd 80 msec earlier then the ri ing point of subglottic pres re Not that the cricothyroid muscle (tensor) triggers acti ity earlier than that of the ocal muscle (adductor)

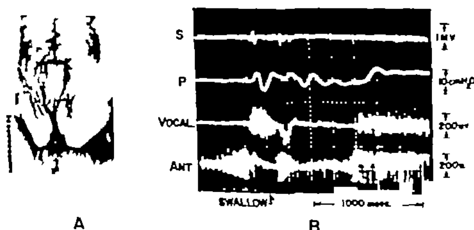


Fig. 4. (A) show the l ryngeal few t time of degl tition (just before igorou sph ncteric closure f the glotti) (B) show relationship of the subglottic pressure chang and the action potential pattern f the laryngeal muscles *S*, so nd; *P* subglottic pressure; *Vocal* EMG of ocal muscl ; *A t* EMG of cricothyroid muscl

the vocal cords assumed the so-called intermediate position one between the lateral and midline positions.

II *Electrical stimulation of the external branch of the superior laryngeal nerve*

Fig 5 B demonstrates the position of the vocal cords when both external branches of the superior laryngeal nerves were stimulated with a frequency of 30/sec and an intensity of 1 volt Both vocal cords became elongated slightly adducted and narrowing the glottis however the vocal cords did not assume the median position even though the frequency and intensity of stimulation were increased This indicates that more adduction as well as elongation of the vocal cords can be obtained by cricothyroid contraction This position of the vocal cords should be referred to as the paramedian position

Upon unilateral stimulation (Figs 5 C and 5 D) the vocal cord of the stimulated side was elongated and the posterior glottal commissure rotated to the opposite side showing homolateral adduction of the vocal cord with retraction of the arytenoid cartilage

When the nerve branch distributed to the oblique part (Fig 5 E) of the right cricothyroid muscle was stimulated the posterior glottal commissure deviated to the opposite side as a result of rotation of the anterior aspect of the cricoid to the side of stimulation and when the nerve branch distributed to the vertical part (Figs 5 F and 1 A) of the right cricothyroid muscle was stimulated the vocal cord of the stimulated side was elongated and adducted

III *Electrical stimulation of the recurrent nerve*

1 Effect of stimulus frequency change (Fig 6) Electrical stimulation was applied on both recurrent nerve stumps with constant intensity of 1 volt and the frequency was changed 1 to 100/sec. Although flicker movement of the vocal cords occured corresponding to each stimulus during low frequency stimulation this flicker movement shifted to smooth abduction of the vocal cords at a frequency of 13–15/sec and the glottis opened wider as stimulus frequency increased and assumed the lateral position when the frequency reached 20/sec

If the frequency raised higher than 30/sec, steadier adduction of the vocal cords started anteriorly assuming the paramedian position at the frequency of 30–35/sec and sphincteric closure of the glottis similar to that observed during deglutition occured Complete closure of the glottis was achieved at the stimulus frequency of 60–70/sec

2 Effect of stimulus intensity change (Fig 7) When the stimulus intensity was changed from 1 to 10 volts at the constant frequency of 20/sec the glottal opening became wider as the stimulus intensity increased and the vocal cords abducted to the extreme lateral position at the stimulus

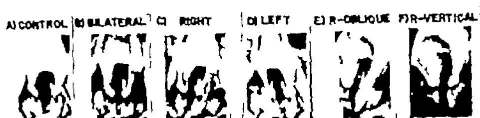


FIG. 5. Fig. 5 shows various laryngeal views when the external branches of the superior laryngeal nerves are electrically stimulated. Stimulation voltage = 1 volt, frequency 30/sec and duration = 0.1 msec. (A) Control. The vocal cords take the intermediate position. Glottal opening is about 5 mm in width. (B) Bilateral. The external branches are stimulated bilaterally. Both vocal cords elongated and adducted to the paramedian position (2 mm glottal width). (C) Right, and (D) left, show the laryngeal views at time of unilateral stimulation of the external branch. (E) R-Oblique. The nerve branch distributed to the oblique part of the right cricothyroid muscle is individually stimulated. The posterior glottal commissure deviated to the opposite side. (F) R-Vertical. The nerve branch distributed to the vertical part of the right cricothyroid [illegible] individually stimulated. Elevation, elongation and adduction of the right vocal cord are noted.



FIG. 6. Fig. 6 shows different laryngeal views when bilateral recurrent nerves are stimulated with various frequencies and constant intensity of 1 volt. Control shows the intermediate position of the vocal cords (5 mm glottal width). The vocal cords abduct to the lateral position at the stimulus frequency of 20/sec (7 mm glottal width) and by increasing stimulus frequency to more than 30/sec, closure of the glottis occurs from the anterior aspect and the arytenoid parts pressing into the epiglottis, glottal opening becomes smaller as stimulus frequency increases (40-50/sec). Complete closure of the glottis occurs when the stimulus frequency reaches 60/sec.

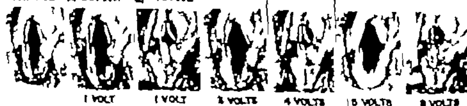


FIG. 7. Fig. 7 shows different glottal views upon the stimulus intensity change. (A) Stimulus intensity increased at constant frequency of 20/sec. Glottal width is 7 mm at 1 volt, 8 mm at 3 volts and 9 mm at 5 volts (extreme lateral position). (B) Stimulus intensity increased at constant frequency of 40/sec. Glottal opening became narrower as the stimulus voltage increased.

the vocal cords assumed the so-called intermediate position one between the lateral and midline positions

II *Electrical stimulation of the external branch of the superior laryngeal nerve*

Fig 5 B demonstrates the position of the vocal cords when both external branches of the superior laryngeal nerves were stimulated with a frequency of 30/sec and an intensity of 1 volt Both vocal cords became elongated slightly adducted and narrowing the glottis however the vocal cords did not assume the median position even though the frequency and intensity of stimulation were increased This indicates that more adduction as well as elongation of the vocal cords can be obtained by cricothyroid contraction This position of the vocal cords should be referred to as the para median position

Upon unilateral stimulation (Figs 5 C and 5 D) the vocal cord of the stimulated side was elongated and the posterior glottal commissure rotated to the opposite side showing homolateral adduction of the vocal cord with retraction of the arytenoid cartilage.

When the nerve branch distributed to the oblique part (Fig 5 E) of the right cricothyroid muscle was stimulated, the posterior glottal commissure deviated to the opposite side as a result of rotation of the anterior aspect of the cricoid to the side of stimulation and when the nerve branch distributed to the vertical part (Figs 5 F and 1 A) of the right cricothyroid muscle was stimulated, the vocal cord of the stimulated side was elongated and adducted

III *Electrical stimulation of the recurrent nerve*

1 Effect of stimulus frequency change (Fig 6) Electrical stimulation was applied on both recurrent nerve stumps with constant intensity of 1 volt and the frequency was changed 1 to 100/sec Although flicker movement of the vocal cords occured corresponding to each stimulus during low frequency stimulation, this flicker movement shifted to smooth abduction of the vocal cords at a frequency of 13–15/sec and the glottis opened wider as stimulus frequency increased and assumed the lateral position when the frequency reached 20/sec

If the frequency raised higher than 30/sec, steadier adduction of the vocal cords started anteriorly assuming the paramedian position at the frequency of 30–35 sec and sphincteric closure of the glottis similar to that observed during deglutition occured Complete closure of the glottis was achieved at the stimulus frequency of 60–70/sec

2 Effect of stimulus intensity change (Fig 7) When the stimulus intensity was changed from 1 to 10 volts at the constant frequency of 20 sec the glottal opening became wider as the stimulus intensity increased and the vocal cords abducted to the extreme lateral position at the stimulus

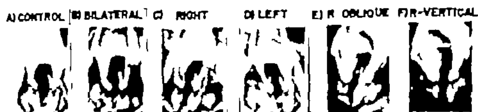


Fig. 5. Fig. 5 show rious laryngeal iew when the external branches of the perior laryngeal nerves re lectricall timul ted. Stimul tion lt ge = 1 olt, frequency 30 sec, and d ration = 0 1 msec (A) Control The ocal cord tak the i termediat position. Glott l peni g is bout 5 mm l width. (B) Bilateral The tern l branches stimulated bilaterally Both ocal cord long ted d dducted t the paramedia position (3 mm glottal width) (C) Right a d (D) left show the laryngeal iew at time of unilateral stim latio f the extern l branch. (E) *R*-Oblique The nerv branch distributed t the bliqu part of the right cricothyroid muscl i indi idually stim lated. The posterior glottal commissure deviated t the opposit side (F *R* Ventral The nerv branch distributed t the rtical part of the right cricothyroid muscl is individ lly stimulated Elev ti n, long tion nd adduction f the right ocal cord re noted.

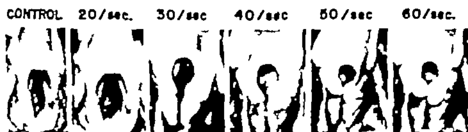
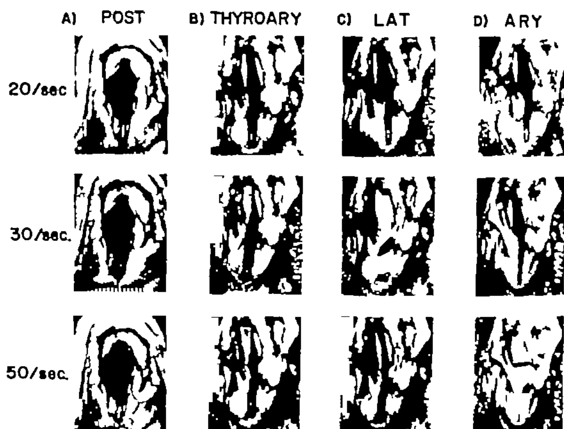


Fig. 6 Fig. 6 show differe t l ryng l iew when bil teral recurrent rves re stimulated ith arious freq encies nd consta t timuli of 1 olt. Control shows the intermediate position f the oc l cord (5 mm glott l w dth The ocal cord bduct t the l teral position t the stim lus frequency f 20 sec (7 mm glottal width nd by ncreasing timul frequency t more tha 30 sec losure of the glott occurs from the nterior aspect nd the rytenoid parts press gai t the epiglottis, glottal opening becomes smaller stimul frequ ncy ncreases (40–50 sec) Complet losure f the glott occurs hen the stim l frequency reaches 60 sec



Fig. 7 Fig. 7 shows different glott l iew pon the stim lus i t ity cha g (A) Stimulus int nsity increased t consta t frequ ncy of 20 sec. Glott l width is 7 mm at 1 lt, 8 mm t 3 lts and 9 mm t 5 olts (extreme lateral position) (B Stim lus inte sity increased t constant frequency of 40 sec. Glottal peni g became narrow the stimulus oltage increased



F o. 8 The recurrent nerve bran hes di t ibuted t ea h i t i l larvngeal muscl n th left id w re stimulated with vari us frequ ncies nd t nstant inten itv f 1 lt (A) P t The n rv b an h to th poste io ri ryt n id muscle on the l ft sid i indi idu lly timul ted The ocal cord on th stimulated id abducted t a lat ral positi n t th frequency of 20/sec nd bdu ti n f th ocal cord took place th stimulu frequ ncy increa ed. Lat al di pl ceme t and d flection of the aryt noid part is obvi us. (B) (C) nd (D) The n rv branches dist ibuted t the l ft thyro-aryt n id muscle (B) l teral cri oarytenoid muscl (C) d ryt n id muscl (D) are stimul ted Th ant rio porti n (B) middl porti n (C) d post rio portion (D) f th l ft vocal cord adduct by incre ing th stimulu frequ ncy Sl ght ddu ti t th timulu frequ ncy f 20 sec and rema kabl dducti n t th stim lu frequ ncy f more than 30 sec re noted Internal di pl cem nt and d flecti n of th ryt id part a e invari bly observed.

intensity of 5 volts If the frequency was kept constant at 40/sec, adduction of the vocal cords always took place as stimulus intensity increased and complete closure of the glottis was observed at the stimulus intensity of 8 volts

IV *Stimulation of the individual branches of the recurrent nerve distributed to each intrinsic laryngeal muscle*

To explore the different glottal movement according to the frequency of the electrical stimulation of the recurrent nerves, stimulation was applied to the nerve branches distributed to each intrinsic laryngeal muscle

1 Stimulation of the nerve branch distributed to the left posterior crico-arytenoid muscle (Fig. 8 A)

When the nerve branch distributed to the left posterior cricoarytenoid muscle was stimulated individually the left vocal cord abducted by increasing the stimulus frequency and assumed the extreme lateral position at a frequency of 20/sec and did not adduct by increasing the stimulus frequency higher than 30/sec.

2 *Stimulation of the nerve branch* distributed to the left thyroarytenoid muscle (including vocalis muscle) (Fig 8 B)

Adduction of the anterior part and shortening of the vocal cord on the stimulated side resulted. Slight adduction of the anterior part of the vocal cord at a stimulus frequency of 20/sec and strong adduction with the stimulus frequency higher than 30/sec were observed

3 Stimulation of the nerve branch distributed to the left lateral crico-arytenoid muscle (Fig. 8 C)

The middle part of the left vocal cord adducted slightly at a frequency of 20/sec and further adduction took place by increasing the stimulus fre*quency higher than 30/sec.*

4 Stimulation of the nerve branch distributed to the left arytenoid muscle (including ventricularis muscle) (Fig. 8 D)

The posterior part of the left vocal cord adducted slightly at a stimulus frequency of 20/sec, and further adduction was followed by increasing the stimulus frequency higher than 30/sec, alth ugh there remained a slight crevice at the anterior part of the glottis. Abduction of the vocal cord was not observed.

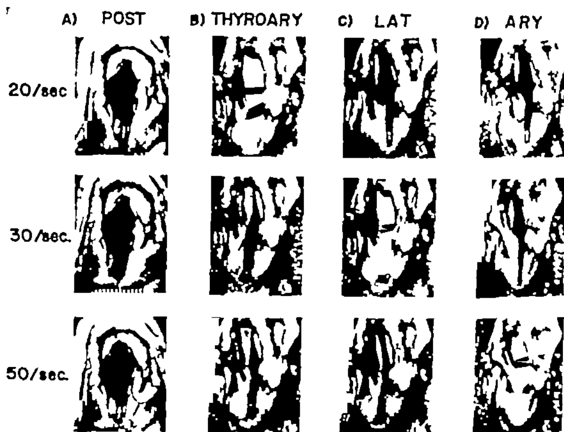
V Simultaneous stimulation of the nerve branches distributed t the posterior cricoarytenoid mu cle (abductor) and each adduct r muscle (Fig 9)

1 Simultaneous timulation of the nerve branches distributed to the right posterior cricoarytenoid and thyroarytenoid muscles (including vocalis muscle) (Fig 9 A)

Although the right vocal cord abducted to the lateral position at a frequency of 20/sec adduction of the anterior part of the right vocal cord was followed by increasing the stimulus *frequency higher than 30/sec.*

2 Simultaneous stimulation of the nerve branch distributed to the right posterior cricoarytenoid and lateral cricoarytenoid muscles (Fig. 9 B) There also occured abduction of the right ocal cord at a frequency of 20 sec and slight adduction of the middle part of the right ocal cord took place by further increasing the stimulus frequency to over 30/sec.

3 Simultaneous stimulation of the right posterio cricoarytenoid and arytenoid muscles (including *ventricularis muscle) (Fig. 9 C)* Abduction of the right vocal cord was observed at a stimulus frequency of 20/sec and adducti n f the posterio part of the right vocal cord occurred as stimulus frequency increased more than 30/sec



F a. 8 The recurrent nerve branches distributed t e ch i trin ic laryngeal muscl n th l ft sid were stimulated with arious frequencies and at con tant inten ity f 1 olt (A) Post: The n rve branch t th posteri r cricoaryten id muscl n the l ft sid is individu lly timulated. The ocal cord n the stimulated id bducted to a lat ral position at th frequ ncy of 20/ ec nd bdu tion of the oc l cord took place a the timulu frequency in reased Lateral d pl cem t nd d flecti n of the ryte-noid part i bvi us. (B) (C) nd (D): The nerv branches distributed t the left th ro-aryt noid muscl (B) l teral crico ryt n id muscl (C) nd ryten id muscl (D) are stimulated Th a t ri r porti n (B) middle porti n (C) nd posterio porti n (D) of th l ft vocal cord dduct by incre i g th stimulu freq n Slight dd cti t th stimulus frequ cy of 20 ec nd rem kabl dd cti n t the timulu freq cy f more than 30/sec re noted Intern l di placem nt nd d flecti f th ryt id part are in l bly bserved

intensity of 5 volts If the frequency was kept constant at 40/sec adduc tion of the vocal cords always took place as stimulus intensity increased and complete closure of the glottis was observed at the stimulus intensity of 8 volts

IV *Stimulation of the individual branches of the recurrent nerve distributed to each intrinsic laryngeal muscle*

To explore the different gl ttal movement according to the frequency of the electrical stimulation of the recurrent nerves, stimulation was applied to the nerve branches distributed to each intrinsic laryngeal muscle



Fig. 10. Upon bilateral stimulation, both vocal cords elongated and adducted to the paramedian position at the frequency of 30/sec (A) and further adduction was followed by increasing stimulus frequency more than 40/sec (B)

VI. *Simultaneous stimulation of the external branch of the superior laryngeal nerve and all adductor nerve branches of the recurrent nerve* (*Fig 10*)

To obtain the vocal cord position similar to the phonatory position, electrical stimulation was applied to bilateral external branches of the superior laryngeal nerves and bilateral recurrent nerve branches distributed to all adductor muscle simultaneously Elongation and adduction to the paramedian position of the vocal cords were observed at a frequency of 25-30/sec (Fig 10 A) and further adduction was followed by increasing stimulus frequency (Fig. 10 B) and complete adduction to the median position was achieved at a stimulus frequency of 60/sec

DISCUSSION

From the electromyographic standpoint, excitation of a few motor units evokes a slight contraction of the muscle and when many motor units discharge vigorous contraction of the muscle results. Respiration for instance is represented by slight contraction of the intrinsic laryngeal muscles, phonation by moderate, and the act of deglutition is one of marked contraction

During quiet respiration the vocal cords are in constant pendulous motion from their neutral or resting position (Intermediate line) In deep respiration, the lateral movement of the cords during inspiration and internal movement during expiration become progressively greater as respiration becomes deeper and more forceful (Pressman & Kelemen, 1955)

Electrical stimulation of the recurrent nerves with a low frequency around 10/sec showed vocal cord contraction corresponding to each stimulus staying within the intermediate line which is similar to the position

A) THYROARY & POST B) LAT & POST C) ARY & POST

10/sec





20/sec





30/sec





50/sec





FIG 9 Th n rv bra hes dist ibuted t the ight post rio cricoaryt id musel (bdu t) d a h dd ct muscle n th ight id ((A) thyroaryt id m scl (B) lateral cricoaryt n d musel (C) ryt noid m scl) re tim l ted im lt eo l

The vocal cord of the t mul ted id abd ct l ghtly t th freq y of 10 sec and marked abd cti n at 20 ec (A) (B) nd (C) re n ted Adducti f th nt ri porti n (A) the middl porti n (B) a d th po t ri port (C) of th oc l cord conversely t kes place the t mulu frequ cy incre ses m re than 30 sec

ment of the vocal cords by homorhythmic impulses conducted through the recurrent nerve. As expected, our results do not support thi theory be cause (1) discharge frequencies of the single motor units in the vocal muscle during phonation did not coincide with vocal pitch, and (2) flicker movement of the vocal cords which was induced by electrical stimulation of the laryngeal nerves cannot be observed when the stimulus frequency increased more than 15/sec.

During deglutition, the action potentials of the cricothyroid muscle ceased at the glottic closure phase of deglutition while the adductors show a vigorous activity On the other hand, complete closure of the glottis similar to that of swallowing was achieved with a *high frequency stimulation of both* recurrent nerves. These results reveal that the cricothyroid muscle does not play the important role for the glottic closure during deglutition

With reference to the mechanism of vocal cord elongation and auxiliary adduction by cricothyroid contraction with stimulation experiments, it elevates the anterior portion of the cricoid ring towards the thyroid car tilage narrowing the cricothyroid distance and elongating the thyroarytenoid distance Consequently the vocal cords are stretched and tensed. This increased tension f the vocal cords moves the vocal process of the arytenoid cartilage medially adducting the vocal cords from the intermediate to the paramedian position.

Unilateral *cricothyroid contraction induces homolateral elongation* and adduction of the vocal cord with deviation of the posterior glottal com missure to the opposite side From Figs. 5 E and 5 F elongation and adduc tion of the vocal cord is mainly due to contraction of the vertical part, whereas opposite deviation of the posterior glottal commissure as a result of rotation of the anterior aspect of the cricoid ring to the side of stimula tion is caused by the backward pull of the oblique part of the cricothyroid on the stimulated side This means that in case of unilateral paralysis, the posterior commisure is deviated to the side of paralysis.

There are some reports which observed vocal cord movement at a time of recurrent nerve stimulation Seymour & Henry (19.4) observed in the cat l rynx that small voltages produced adduction movement of the glottis *and with increasing strength of stimulus*, an adductor "flick could be observed followed by an active abductor movement.

Murtagh & Campbell (194) also obtained only adduction in similar ex periment on the goat s larynx. Williams (1951) observed only adduction with minimal stimuli on human recurrent nerves.

Capps (19.8) observed the following results in human larynx. Recurrent nerve timulation at 10 volts and 8 pulses/sec induced adductor flicks timulation at 10 volt and 25 pulses/sec induced steadier adduction and stimulation f 50 volts and 25 pulses/sec produced abduction. These results reveal that the ocal cords showed a different movement with increasing timulu (voltage) strength at constant frequency

From our observ tion, while alternation of the stimulu strength showed

of quiet respiration When the stimulus frequency reached 20/sec, the vocal cords assumed the lateral position which is similar to the deep inspiratory position On the other hand when the external branch of the superior laryngeal nerve was bilaterally stimulated (Fig 5 B) at a frequency of 25–30/sec, the vocal cords assumed the paramedian position similar to the deep expiratory position These results are in close agreement with the findings of Nakamura *et al* (1958) that is, during respiration many of the continuously discharging single motor units of the laryngeal muscle increased their frequency from the range of 5–10 impulses/sec during rest, to the range of 10–20 impulses/sec during contraction and sometimes to the range of 50–60/sec

During phonation there exists the latent time between the first visible appearance of the action potentials, the beginning of subglottic pressure development and the subsequent audible onset of phonal function During this latent time, the laryngeal muscles bring the cords into proper position and tension for each vocal performance before expiratory air stream begins to set them into vibratory motion Since low pitch voice production within average speech range (chest register) is due to repeated opening and closing movement of the vocal cords, usual speaking voice requires little cricothyroid activity On the other hand, in higher pitch voice production (head register) the vocal cords elongated and strained and vibration is observed only along the inner edge of the vocal folds (Kirikae, 1943 Luchsinger & Arnold 1949)

Whine is a high pitch tone and corresponds to the head register and action potential of the cricothyroid muscle fired before the adductors Concerning whine, tension of the vocal cords takes place first and then adduction to the phonatory position occurs This same movement of the vocal cords was observed at a time of simultaneous stimulation of extrinsic superior laryngeal nerves and all adductor nerve branches of the recurrent nerves (Fig 10) The tension and adduction to the paramedian position of the vocal cords were observed at the stimulus frequency of 30/sec and then further adduction to the median position was achieved with frequencies higher than 40/sec

The discharge frequency of single motor units of the adductor and tensor muscles during phonation increased when compared with that during respiration Katsuki (1950) reported that with rising pitch the discharge frequency of the cricothyroid muscle increased until 20–40 impulses per second for the highest tones of falsetto voice Faaborg Andersen (1957) described a similar discharge frequency of a single motor unit ranging from 3 to about 30 per second Urata (1960) reported maximal discharge frequency of single motor units in the vocal muscle was 60/sec during phonation These discharge frequencies are of course much lower than the vibratory frequencies in cycle of the audible tone

According to Husson's neurochronaxic theory (1950) the frequency of vibration of the vocal cords at given pitch of voice is due to active move-

ment of the vocal cords by homorhythmic impulses conducted through the recurrent nerve. As expected, our results do not support this theory because (1) discharge frequencies of the single motor units in the vocal muscle during phonation did not coincide with vocal pitch, and (2) flicker movement of the vocal cords which was induced by electrical stimulation of the laryngeal nerves cannot be observed when the stimulus frequency increased more than 15/sec.

During deglutition, the action potentials of the cricothyroid muscle ceased at the glottic closure phase of deglutition while the adductors show a vigorous activity. On the other hand, complete closure of the glottis similar to that of swallowing was achieved with a high frequency stimulation of both recurrent nerves. These results reveal that the cricothyroid muscle does not play the important role for the glottic closure during deglutition.

With reference to the mechanism of vocal cord elongation and auxiliary adduction by cricothyroid contraction with stimulation experiments, it elevates the anterior portion of the cricoid ring towards the thyroid cartilage, narrowing the cricothyroid distance and elongating the thyroarytenoid distance. Consequently the vocal cords are stretched and tensed. This increased tension of the vocal cords moves the vocal process of the arytenoid cartilage medially adducting the vocal cords from the intermediate t the paramedian position.

Unilateral cricothyroid contraction induces homolateral elongati n and adduction of the vocal cord with deviation of the posterior glottal commissure to the opposite side. From Figs. 5 E and 5 F elongation and adduction of the vocal cord is mainly due to contraction *of the vertical part*, whereas opposite deviation of the posterior glottal commissure as a result of rotation of the anterior aspect of the cricoid ring to the side of stimulation is caused by the backward pull of the oblique part of the cricothyroid on the stimulated side. This means that in case of unilateral paralysis, the posterior commissure is deviated to the side of paralysis.

There are some reports which observed vocal cord movement at a time f recurrent nerve stimulation. Seymour & Henry (1954) observed in the cat larynx that small voltages produced adduction m vement f the glottis nd with increasing strength of stimulus, an adductor "flick" could be observed followed by an active abductor movement.

Murtagh & Campbell (1943) also obtained only adduction in similar experiments on the goat's larynx. Williams (1951) observed only adduction with minimal stimuli on human recurrent nerves.

Copps (1958) observed the f llowing results in human larynx. Recurrent nerve stimulation at 10 v lts and 6 pulses/sec induced adductor flicks, stimulation at 10 volts and 25 pulses/sec induced steadier adduction and stimulation of 50 volts and 25 pulses/sec produced abduction. These results reveal that the vocal cords showed a different movement with increasing stimulus (voltage) strength at constant frequency.

From our observation, while alternation of the stimulus strength showed

different glottal movement, by contrast, the effect of glottal movements was very dramatic with constant stimulus strength but increasing frequency change (Figs 6 and 7)

Looking at the different movement of the vocal cords depending upon the frequencies of the recurrent nerve stimulation if the nerve branch distributed to the posterior cricoarytenoid muscle was stimulated individually the vocal cords abducted to the extreme lateral position at a frequency of 20/sec and adduction of the vocal cords can not be seen even though the stimulus frequency increased higher than 30/sec.

On the other hand when the nerve branches distributed to each adductor muscle was individually stimulated, only adduction of the vocal cords was observed i e., slight adduction of the vocal cords occurred at the frequency of around 20/sec and further adduction was followed by increasing stimulus frequency more than 30/sec.

Further if the stimulation was applied to the nerve branches distributed to the posterior cricoarytenoid muscle and each individual adductor muscle simultaneously abduction of the vocal cords occurred at a frequency of 20/sec and adduction of the vocal cords invariably took place by increasing the stimulus frequency more than 30/sec

Thus the posterior cricoarytenoid muscle has a tendency to respond to the lower frequency impulses, when compared with the adductor muscles and that of the cricothyroid muscle is between that of the abductor and adductors

These results show that there are different impulse frequencies to induce the effective contraction of each abductor and adductor muscle, that is from a viewpoint of vocal cord movement, maximum tension of the posterior cricoarytenoid muscle occurs at a frequency of 20/sec, while higher frequencies are needed to achieve maximum tension of the adductors In other words, the adductor muscles have high frequency characteristics compared with the abductor muscles. The larynx opens with lower frequency stimulus (fewer motor units discharge) or acts as a sphincteric valve with higher frequency discharges (many motor units discharge)

CONCLUSION

1 During quiet respiration, the vocal cords are slightly abducted with inspiration and slightly adducted with expiration about the intermediate line. Electromyogram showed action potential of the abductor muscles is more active during inspiration while the adductors increase their activity during expiration

2. During phonation (whine) the vocal cords are elongated and assumed the median position Electromyogram showed considerable discharge in the cricothyroid muscle (Tensor) and the adductors. The cricothyroid muscle triggers activity earlier than that of the adductors.

3 During deglutition, both vocal cords adduct from the anterior aspect and shorten and the arytenoid part is pressed against the epiglottis and strong sphincteric closure of the glottis occurs. The adductors showed strong electrical discharge during glottal closing phase of deglutition, while the cricothyroid muscle ceases electrical activity at this time

4 Bilateral stimulation of the external branch of the superior laryngeal nerve induced elongation and adduction of the vocal cords to the para median position by increasing stimulus frequency to 25–30/sec.

5 Unilateral stimulation of the external branch of the superior laryngeal nerve induced deviation of the posterior glottal commissure to the opposite side

6 Unilateral stimulation of the nerve branch to the vertical part of the cricothyroid muscle induced homolateral elongation and adduction of the vocal cord.

Unilateral stimulation of the nerve branch to the oblique part of the cricothyroid induced deviation of the posterior glottal commissure to the opposite side

8 Bilateral recurrent nerve stimulation induced abduction of the vocal cords to the lateral position at a frequency of 20/sec. Adduction of the vocal cords took place by increasing stimulus frequency more than 30/sec and complete closure of the glottis was achieved at a stimulus frequency f 60–70/sec.

9 Increase of the stimulus strength at constant frequency of 20/sec induced abduction of the vocal cords to the extreme lateral position, and increase of the stimulus strength at constant frequency of 40/sec induced glottal closure

10 Individual stimulation of the nerve branch to the posterior crico-arytenoid induced only abduction and assumed the extreme lateral position at a frequency of 20/sec.

11 Indi idual stimulation of the nerve branch distributed to each ad-duct r muscle induced slight adduction of the vocal cords at a frequency of 20/sec nd strong adduction with the stimulus frequency more than 30/sec

12. Simultaneous stimulation of the nerve branch distributed to the ab-ductor and each adductor muscle induced abduction of the vocal cords at a stimulus frequency of 20/sec and adduction of the vocal cords invariably took place as stimulus frequency increased more than 30/sec.

13 Simultaneous stimulation of the external branch of the superior laryngeal nerve and all nerve branches distributed to the adductors induced vocal cord elongation and adduction to the paramedian position at a fre-quency of 25–30/sec and further adduction to the median position occurred with the timulus frequency mor than 40/sec.

RÉSUMÉ

Nous avons étudié les mouvements des cordes vocales chez le chien pendant la respiration et la phonation (hurlement) Nous avons déterminé les fréquences de stimulation pour l adduction et la fermeture de la supraglotte Nous avons comparé une greffe musculo nerveuse du nerf larynge récurrent et la réanastomose d autres portions du même nerf

ZUSAMMENFASSUNG

Die vorliegenden Untersuchungen betreffen die Stimmbandbewegungen von Hunden während Atmung und während Phonation (Winseln) Das Verhältnis von Reizfrequenz zu Adduktion und Verschluss der Supraglottis wurde geprüft Ferner wurden Untersuchungen von gestielten Nerv Muskeltransplantaten des Nervus recurrens und Reanastomosen der übrigen Anteile desselben verglichen

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St Loui M U S.A

DISCUSSION

F Brunetti J félicite va t tout M. Ogura pour l'intéressante documentation scientif qu qu il a présenté et demand s'il f it aussi des expéri nces électro-micrographiques avec des curares, comme on a déjà fait dans la Clinique ORL de Turi pou étudier le comportement très différent entre muscles et phonations vers les phenomènes d dépola isation et d repolarisation provoqués pa ces substances pharmacologiques.

A Laskiewicz As for the paramedian position of the vocal cord, I would like t mention that Ant. Jura (L. von Poland) in 1906 wa th first who had theoretically suggested that this position is due not only to a lesion f the recur rent nerve of the sick concerned but that the *superio lary geal nerve is to be* contemporary involved. In 1924 Gusta Hofer (Vienna) had experimentally on nimals proved that the named position of the vocal cord is due to lesion of the recurrent nerve a d the section f the superior laryngeal nerve simultane-ous!

M Barr tt H M Ogura noticed in hi experiments on d glutition move ments f the epiglottis.

J H Ogura (Reply) t Mr *Brun tti* We did n t study vocal cord movement *and effect of drugs.*

to Mr *Laskiewicz* I am familiar with the statement that a lateral position is due to injury f the recurrent laryngeal nerv and di ision of the superior laryngeal nerv These studies were made in animals to gain insight int the problem of

RESUME

Nous avons étudié les mouvements des cordes vocales chez le chien pendant la respiration et la phonation (hurlement) Nous avons déterminé les fréquences de stimulation pour l adduction et la fermeture de la supraglotte Nous a ons comparé une greffe musculo-nerveuse du nerf larynge récurrent et la réanastomose d autres portions du même nerf

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Die vorliegenden Untersuchungen betreffen die Stimmbandbewegungen von Hunden während Atmung und während Phonation (Winseln) Das Verhältnis von Reizfrequenz zu Adduktion und Verschluss der Supraglottis wurde geprüft. Ferner wurden Untersuchungen von gestielten Nerv Muskeltransplantaten des Nervus recurrens und Reanastomosen der übrigen Anteile desselben verglichen

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COMPARISON BETWEEN NEURAL AND PSYCHOPHYSICAL RECORDINGS OF TASTE STIMULATIONS

H. Diamant, M.D.

From the Department of Otorhinolaryngology, University of Umeå, Umeå, Sweden

In a series of experiments in man it is possible to show the very strong resemblance between the neural recordings established during operation and the preoperative findings at psychophysical stimulation.

For many years, the former head of the Physiological Department of the Veterinary School in Stockholm, Professor Yngve Zotterman, has done research on the sense of taste. His experiments started over forty years ago and he has continuously and consistently fulfilled his experiments in different ways to solve problems connected with taste.

The experiments were, in the beginning, performed on different animals, but at the end of the fifties Professor Zotterman tried, together with Doctor Ahlander of the Southern Hospital in Stockholm, to record from the chorda tympani in humans. The experiments were, for different reasons, not successful, and were later transferred to the Karolinska Hospital, where I together with Professor Zotterman succeeded in making some recordings from the chorda tympani. These experiments were continued at the Ear Department of the Karolinska Hospital, where there was a very well shielded room in which a series of recordings were taken from the chorda tympani.

It is fortunate that, by a freak of nature, impulses from the tongue to the brain pass in the chorda tympani through the middle-ear. Thanks to the very rapid development of middle-ear surgery, especially surgery for stapes and the oval window, the chorda tympani has become easily available for examination. In many cases the chorda tympani is an obstacle to the surgeon on his way to the stapes, and has to be cut. It seemed that patients did not have very much trouble from this divided chorda. Anyway, they very seldom complained of this trouble, and above all the troubles were so small in comparison with the very great gain in hearing that they did not mention them.

To be able to successfully record from the chorda tympani some conditions must be fulfilled. First of all, one must have a very good electrically shielded room. Secondly, all the preoperative examinations of the taste of the patient have to be very thorough. Professor Zotterman has a lot of experience here. We have also used the experience of psychologists working with psychophysical examinations of taste. The third condition is, of course, that you have the ethical justification for these experiments. The patient who is operated upon will only have the operation-time prolonged

reinnervation in our experiments with replantation and transplantation of the larynx Reinnervation will be important for maintenance of vasomotor tone as well as movement of the vocal cords. Thus we need information on frequency stimulus response of each nerve branch and vocal cord movements for our control study

to Mr *Barretto* There was some posterior movement of the epiglottis but these observations were made through an anterior pharyngotomy approach which would make these findings less significant Movement of the epiglottis can be nicely observed by cine-radiographic studies of deglutition and on phonation

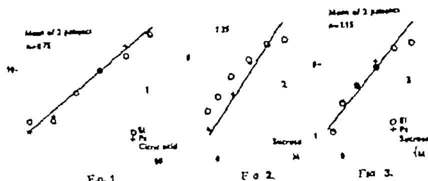


Fig. 1 Relati psy hophy ical (*Ps*) nd lectrical responses (*El*) t citric acid. Mean of 2 patients.

Fig. 2. See text.

Fig. 3 Relatio bet en psy hophysic l (*Ps*) nd lect ical responses (*El*) t sucrose Mean of 2 patients.

When we did consider the results of the experiments it seemed that most of what we tried to prove had been achieved But since then we have made a very thorough examination of what generally happens with patients who ha e their chorda tympani divided and we found that many of the patients in fact have more trouble than earlier investigators thought and even if the troubles in many cases are insignificant they are serious enough You thus have t take these complications into consideration when you are per forming the operation for stapes-surgery That means that one must try to a oid damaging the chorda tympani and that experiments should be per formed on undivided chorda tympani. Because of this, we have constructed a micro-manipulator with which it is possible to reach the chorda tympani and put a micro-electrode in it for direct recordings. In this way the recording will be taken from a very small strand of the nerve instead of from the whole nerve—if you are lucky So f r we are just at he beginning of this work, which is very tedious and will take a long time, but which we hope will get still better results than those we have obtained so far

RESUME

Da s un séri d'expériences hez l'homme la stimulation gustative nerveuse pendant l opér tion a ét comparée à la stim lation psychologique a ant l opération

ZUSAMMENFASSUNG

I iner Serie von Versuch n m Menschen kann man eine stark Gleichheit beobachten zwischen den neuralen Registrierungen, erhalten bei Operationen un l den praoperativen Beobachtungen bei psychophysikalischer R izung.

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one hour We can keep the time down by good planning, so the trouble the patient will have is just the cut chorda which is something which will happen anyway in a lot of cases

The early investigations gave valuable information about the relation between the strength of the gustatory stimulus and the recorded summated responses from the human chorda to various taste solutions Working on human subjects offers the possibility of collecting information not only on the relationship between gustatory stimulus and the neural response but also on the relation between the neural and psychophysical responses.

When I left Stockholm for Umeå we could continue the research already begun, especially since we succeeded in putting up an electrically shielded metal-cage inside one of our operating theatres We started the work with Docent Borg who is assisting professor in clinical psychology and who made the psychophysical investigations That was the beginning of a series of experiments which were performed to make a comparison between the neural and psychophysical responses to gustatory stimuli

During 1965-1966 we performed experiments in 18 cases The results were very promising especially on two occasions, October 1965 and February 1966 The last experiments in August 1966 confirmed the results. The psychophysical examinations were performed two days before the operation using citric acid NaCl and sucrose The method of magnitude estimation was used This method was introduced by Stevens and requires that the subjects can handle numbers and make quantitative estimations on the ratio level In a pre-experiment all patients had to make estimations of surfaces of different sizes so that we could screen out those who obviously could not make magnitude estimations The same stimuli and the same random order of presentation were used in the electrophysiological experiments. The stimuli were presented in pairs, the standard with one comparison stimulus To test the method psychophysical experiments of the same kind using salt and citric acid were made on 14 young students Straight lines may be adjusted to the values it means that a power function may describe the relations The Fechnerian log function does, however better describe the variation in neural activity If as a first rough estimation, we describe both the neural and the psychophysical responses with power function we find an astonishingly good agreement The exponent of the psychophysical function $n_s = 0.5$ is the same as that of the neurophysical function $n_r = 0.5$

We succeeded in obtaining from 2 patients (I J and S P) subjective estimations as well as electrical responses to sucrose and citric acid Fig 1 shows the relative psychophysical and electrical responses to citric acid and they are plotted in a log log diagram Fig 2 gives the relations for sucrose for 3 patients Each point is the median of three observations in each series of tests on the same individual How well the psychophysical functions follow the neural will be seen from Fig 3 where the diagram gives the functions of the mean values obtained for two of the patients

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ON THE IMPORTANCE OF TRACE ELEMENTS FOR MUCOSA OF UPPER AIR PASSAGES

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Serum iron level was determined in 31 scleroma patients (20 previously cured with antibiotics, 2 requiring further treatment and 3 untreated) The determinations were performed in fasting patients and 3 and 6 hours after oral administration of 180 mg of ferric sulphate In 20 of them the serum copper level was determined too. In 29 subjects the serum iron content was fou d to be und r bottom norm, in 13 of 20 subjects examined for serum copper there were also found low values differi g from the normal one.

Until quite recently the only disease entity in our speciality the development of which stood in association with iron deficiency was the Plummer Vinson syndrome

In 1960, Bernat drew attention to the significance of iron deficiency in the pathogenesis of ozena. In his monograph, published in 1965 he presented convincing data, based on a large clinical and experimental material, in support of this opinion.

Histological pictures of mucous membrane of the upper respiratory tract in laboratory animals fed on a diet deprived of iron are very con incing The metaplastic changes in epithelium, atrophy of mumous glands and changes in the connective tissue layer of mucosa resemble very much those in the histological picture of nose mucosa in patients with ozena. His ttempts at treating ozena with iron proved encouraging

We checked the results of Bernat s investigations and found them to be correct.

Then arose the question, if there are any other morbid conditions giving changes in the respiratory tract due to iron metabolism disturbances in the body and whether it is only the iron metabolism that is disturbed or perhaps there are also some other trace elements involved which are deficient or excessiv In those morbid conditions. In the first stage of our investigations, imed at answering the above questions, we studied a disease th tiopathology of which is still obscure, although the entity was described nearly 100 years ago It is scleroma, a disease of the upper respiratory tract, in which the specific granulation is undoubtedly due to the nfecti n by a microorganism specific to this disease A proof of this is the efficacy of treatment with appropriate antibiotics and the behaviour of

DISCUSSION

M Portmann Vous obtenez une réponse pour l eau froide et pas de réponse pour l eau à température ordinaire Pensez vous que cela prouve qu il y a beaucoup de fibres sensitives dans la corde du tympan? J ai en effet travaillé les nerfs de l oreille et la corde du tympan en utilisant des techniques histologiques et je n ai trouvé que très peu de fibres de type sensitif beaucoup de fibres de type sensoriel et végétatif (Il s agissait de techniques nerveuses spéciales permettant des différences tinctoriales selon la nature des fibres)

H House The recent discussions at Oxford referred to by Mr Diamant indicated 30% to 40% of the cases for stapes surgery required sectioning of the chorda tympani to obtain adequate marking exposure In our experience after 4 months 5% of the cases that have an undisturbed nerve at surgery have taste disturbance apparently due to fibrosis (revealed by section of the nerve on subsequent revisions) 7% have taste disturbance if the nerve is sectioned and 15% have taste disturbance if the nerve is stretched From a subjective clinical viewpoint it seems better to section rather than to stretch the nerve This same phenomenon is observed in regard to dryness of the mouth especially in post menopausal patients.

Would Mr Diamant please comment on this apparent compensatory phenomenon—what might be the compensatory pathway?

F Escher Can something be done after bilateral loss of the sense of taste caused by damage of the chorda?

H Diamant (Reply) to Mr *Portmann* Of course the chorda tympani contains sensory and/or sensitive fibres. Anyway they contain fibres sensitive to temperature and to touch. In fact, we use touch to test the experimental arrangement. In a nomogram of the chorda tympani made by Costen it seems clear that it must contain sensitive fibres.

to Mr *House* I am not sure that a compensation objectively ever happens when the chorda tympani is cut What happens to chorda tympani after operation is that the taste seems disturbed forever Not so subjectively There is also a great difference between people according to the sense of taste Some will never have any trouble and if they are psychophysically examined before operation one often finds a very week reaction to different sapid solutions

The reason why patients bilaterally operated complain of dry mouth is probably that the submandibular glands in such high degree provides for the moistness of the oral cavity It has constant flow of saliva in contrast to the parotid glands which only secrete on stimulation

to Mr *Escher* There is no possibility of restoring the function of the chorda tympani according to taste It is too sensitive We have for instance never succeeded in splitting the nerve to get recordings from finer strands of the nerve

This opinion is corroborated by a higher incidence of scleromatous infection in women of the age at which the iron deficiency appears.

It is not excluded that the endemic occurrence of scleroma in some regions is connected with a poor iron content in the water of those regions and consequently in the food of the population li ing there Investigations in this direction should be taken up

A less distinct copper drop in the serum of patients (in 13 cases out of 20 examined) seems to speak for the smaller importance of the deficiency of this element in the pathogenesis of atrophic changes in the mucous membranes of the respiratory tract.

Similar disturbances of iron metabolism in ozena and scleroma may indicate some relationship of the two diseases, expres ing itself also in the allied bacterial flora found n mucous membranes of the respiratory tract in both diseases and in very similar clinical pictures of ozena and atrophic f rms of scleroma.

The future will show if the exact knowledge of the relation between the deficiency of some trace elements, especially iron and the changes in the mucosa of the respiratory tract will bring us nearer to an explanation of the etiopathology of the morbid conditions mentioned here and perhaps it will also contribute to a better knowledge of the development of some other diseases in ur speciality

RESUME

Chez 31 malades scléromateu (20 guéris par des antibiotiques, 2 exigeants du tra tement *supplémentaire et 3 non traités) on a déterminé le ni eau du fer dans* le serum à jeun et 3 et 6 heures près l'administratio par la bouche d 180 mg d sulfat de fer Chez 20 malades d entre eux on a déterminé l contenu de cuivre d ns le sérum Chez 29 examinés on a constaté l contenu du fer considérablement bai se par rapport à la limite i férieure de la norme che 13 d'entre 20 examinés pour le cont nu de cu vre d ns le sérum on co staté aus i les leurs minimales, différentes d la n rme

ZUSAMMENFASSUNG

An 31 Sklerom-P tienten wurde der Fe-Spi gel im Serum bestimmt. V n diesen P tient n ware 26 aus durch Antibiotika usgeheilt worden 2 erforderten me w tere Behandlung und 3 ware bisher unbeha d lt Die Untersuchungen wurden an den Patienten im fastenden Zustand und 3 und 6 St nden nach oraler Verabr ichu g on 180 mg Ferrisulf t durchgeführt. An 20 der P tienten wurde h der Cu-Spiegel im Serum bestimmt. Es ergab sich dabei, dass bei 29 der Patienten der Eisengehalt im Serum u terhalb der nteren Normgrenze lag und das be 13 von den 20 a f Kupfer untersuchten Patienten auch der Kupferspiegel im Serum zu niedrige W rte zeigte

serum reactions in patients with scleroma, the latter being an expression of antigenicity of a microorganism from the Klebsiella group The patients with scleroma in its typical forms are found as a rule, in certain definite areas of the world but the cases of its atypical abortive forms mostly un diagnosed are scattered all over the countries of both hemispheres.

The etiopathologic obscurity of scleroma consists in the fact that the very infective agent does not account for the development of the disease There must coexist another exo- or endogenic factor A contact of many years of a patient with a healthy individual may not bring about any infec tion of the latter but under other conditions, even a short standing contact may result in the infection of the healthy individual A husband hardly ever becomes infected by his wife Men on the whole suffer from the disease less frequently than women do Daughters of mothers with scle-roma often themselves fall ill with the disease

Another puzzling moment in the pathogenesis of scleroma was the fact of a frequent association of hypochromic anemia which used to be ac counted for as the result of a specific infection

We pointed out that this explanation was wrong At the meeting of our Collegium held in Edinburgh in 1963 I presented a paper in collaboration with Dr Durska Zakrzewska based on the largest material ever published in which the possibility of an entire cure in 70 per cent of scleroma cases was pointed out on the basis of all the hitherto known criteria of curability

In a group of 26 cured patients we compared the hemoglobin values of the period before cure with those determined at different times after the cure was completed, i e after the eradication of the specific infection No essential difference was stated between the values found before and after cure which contradicts the statement of an infective origin of anemia It is to be stressed however that among the patients cured we did not find so very low hemoglobin levels, before starting the treatment, as other authors did in their scleroma patients

On assuming that the endogenic factor facilitating the specific infection in some individuals is a deficiency of iron and perhaps also of some other trace elements in the body we took up their determinations in the sera of scleroma patients and of those already cured of the disease

Out of 31 persons (including 12 males) only in two cases was the serum iron normal. In all the others the iron values were much below the bottom limit recognised a the norm for either sex

In some cases of patients cured we observed iron values as low as 40 γ or even 30 γ in fasting patients and rather high ones at 3 and 6 hours after oral load with 180 mg of ferric sulphate The high iron binding capa city of the serum of scleroma patients and the very low values of the coefficient calculated from iron content in the serum of fasting scleroma patients and its iron binding capacity allow us to draw a conclusion that this primary iron deficiency in the body which is demonstrable even after elimination of the infective agent is the very factor facilitating infection

This opinion is corroborated by a higher incidence of scleromatous infection in women of the age at which the iron deficiency appears.

It is not excluded that the endemic occurrence of scleroma in some regions is connected with a poor iron content in the water of those regions and consequently in the food of the population living there. Investigations in this direction should be taken up.

A less distinct copper drop in the serum of patients (in 13 cases out of 20 examined) seems to speak for the smaller importance of the deficiency of this element in the pathogenesis of atrophic changes in the mucous membranes of the respiratory tract.

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The future will show if the exact knowledge of the relation between the deficiency of some trace elements, especially iron, and the changes in the mucosa of the respiratory tract will bring us nearer to an explanation of the etiopathology of the morbid conditions mentioned here and perhaps it will also contribute to a better knowledge of the development of some other diseases in our speciality.

RÉSUMÉ

Chez 31 malades scléromateux (26 guéri par des antibiotiques, 2 exige nts du traitement supplémentaire et 3 non traités) on a déterminé le niveau du fer dans le sérum à jeun et 3 et 6 heures près l'admi istrat on par la bouch de 180 mg d sulf t d fer. Chez 20 malades d ntre eux on a déterminé le cont nu de cuivre dans le sérum. Chez 29 xaminés on a constaté l contenu d f r considérablement abaissé par rapport à la limit inférieure de la norme, chez 13 d'entre 20 examinés pou le contenu d cui re dans le sérum on a constaté ussi les aleurs minimales, differentes de la norm

ZUSAMMENFASSUNG

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A Zakr-ewski M.D
40 Pr-ybys-ewski St Po nan, Poland

DISCUSSION

G Bustamante We have in Mexico one big zone of ozena and rhinoscleroma and have never found a close relation except the geographical distribution Is it possible to confuse the atrophic state of rhinoscleroma with ozena? Maybe the lower intake of protein has some intervention on the process? The predominance of ozena and rhinoscleroma in people with Indian blood is for me apparent.

I Friedmann Mr Zakrzewski has very kindly examined the sera of several patients seen in London and suspected of scleroma These were all negative Does he rely on electron microscopy for diagnosis? Does he relate scleroma and malignant granuloma?

A Zakr-ewski (Reply) I only indicated the relationship between ozena and scleroma because we had the opportunity to observe not only a number of cases of ozena among the cases of scleroma in the same families but also the effect of treatment by an iron given intravenously is similarly encouraging As to electron microscopy for diagnosis I have no personal experience In my opinion scleroma and malignant granuloma are quite different entities

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POSSIBLE VASCULAR REGULATORY MECHANISMS IN THE MUCOUS MEMBRANE OF THE UPPER RESPIRATORY TRACT

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These regulations take place, above all, in the vascular system and are caused by vegetative-nervous irritations. The principle of regulation in which the arteriovenous anastomoses, being controlled by the nervous system, are considered as effectors is explained. In this connection hypoxia of tissue together with the infiltration of lymphocytes and plasmacells, play an important part.

Basically the terminal section of the vessels supplying the mucous membrane of the upper respiratory tract may be divided into three parts. The first part comprises the larger afferent and efferent vessels, the second the vascular regulatory systems, i.e. the precapillary arterioles and the arteriovenous anastomoses with their blocking and reducing valves, and the third the network of capillaries.

The network of the capillaries maintains the metabolism—both maintenance and functional—of the cells and tissues. It supplies via the internal circulation both the interstitial tissues and the parenchymatous elements of the mucosa, as required. The control of the capillary activity in the case of constant blood flow through the larger arteries, is logically explained by the activity of the arteriovenous anastomoses. This paper will, therefore lay particular stress on the vascular shunts, their localization, morphology functions, and influence upon capillary and internal circulation of interstitial fluid.

Although the occurrence of arteriovenous anastomoses in the mucous membrane of the upper airways appears to be a common phenomenon, we nevertheless did our own histological studies on them, with the object of detecting morphological elements of a regulatory system in the mucosa, which on the one hand would be connected with the nervous, and on the other with the vascular system. The existence of such a regulatory system seems very probable since an increase in glandular secretion in combination with a filling of the cavernous tissue—and the inverse processes, a decrease in glandular secretion combined with a decongestion of the mucosa—are anything but purely accidental phenomena. Rather we should term them a defective functioning of the regulatory system normally operating according to plan under regular conditions.

Parts of the mucosa from the septum in the vicinity of the boundary between ciliated and squamous epithelium were obtained fresh and fixed

in zinc iodine-osmium according to Champy (1963) as well as in formol, dehydrated by means of terpineol and embedded in paraffin Serial sections were stained partly with hematoxylin eosine, and partly according to Pasini (Romeis) combined with nuclear staining according to Hansen (Romeis) Graphic reconstructions of arteriovenous anastomoses were obtained from the serial sections

The histological examination of the above mentioned areas of human mucous membranes yielded the following findings There were no nervous receptor elements of a regulatory system such as organized terminal bodies or any other conspicuous nervous formations, in the areas investigated On the other hand effector elements, amongst which we include the arteriovenous anastomoses were present in great numbers The number of arteriovenous anastomoses found were related to the volume of the specimen examined Independently of the size of the mucous membrane specimen the relative mean distance from one anastomosis to the next was calculated to be between 1 3 and 1 4 mm In the regions of the nasal mucosa studied the incidence of anastomoses was dependent on only one factor the size of the object studied

Arteriovenous anastomoses are variously situated in the mucosa They are however predominantly located at a depth of 1–3 mm, so that they may be said to be located immediately before the terminal portion of the vascular system

The vascular shunts vary morphologically ranging from simple direct connections from an arterial branch—which is, of course equipped with some flow-controlling system—into a venous branch to the highly complex forms of Hoyer-Grosser (Clara) organs (Fig 1) with gradual transitions between these extremes In the last mentioned forms, just as in the neuro-myo-arterial glomera in the skin, it is possible to show after zinc iodine-osmium fixation nervous fibres as well as fibrillar nervous *reticulum* within the connective-tissue sheath covering the anastomosis. However all these formations clearly correspond to the descriptions given elsewhere in the literature There are numerous indications of the functional significance of the arteriovenous anastomoses in the nasal mucosa We shall in the following briefly explain the influence of the arteriovenous anastomoses on the peripheral vessels The interstitial lymph passages begin at the arterial branch of the capillary i e where the capillary filtrate is produced and end in the venous branch of the capillary where at least the major part of the interstitial lymph returns into the bloodstream The hydrodynamic pressure is of controlling importance for the production of capillary filtrate Any change in tension will therefore result in a change in the amount produced and probably also in the composition of the capillary filtrate It will also have an influence upon the nutrition as well as the functioning of the mucous membrane The hydrodynamic pressure in the arterial branch may however be greatly affected by the activity of the vascular shunts At a constant blood flow an opening of the connecting

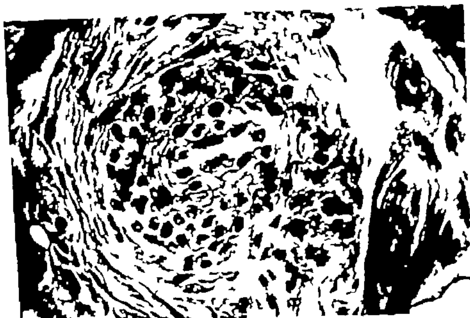


Fig. 1. Glomus-like bodies of arteriovenous anastomosis i the mucous membrane f the nose.

branch of the anastomosis will result in a drop in the pressure in the capillary vessels situated peripherally from the anastomosis, whilst closure of the connecting branch will cause a pressure rise. Normally the connecting branches of the anastomoses will be constricted and dilated at intervals ranging between 2 and 30 seconds. Temporary complete contractions or dilatations may within certain limits still be considered to form part of the normal regulatory functions of an anastomosis. A permanent opening or closure of a vascular shunt, however will result in an equally permanent reduction or increase in the interstitial tension and, in consequence in a depression or overstimulation of tissue functions. In view of the profusion of vascular shunts in the nasal mucosa it seems more probable that drugs which influence the vasomotor functions act upon richly innervated arteriovenous anastomoses, rather than on the capillary vessels themselves. If one assumes that the therapeutic measures reach the arteriovenous anastomoses and consider in this connection also the factors of hydrostatic pressure capillary fluid exchange and the control of the internal circulation, this would explain the pathological changes found in vasomotor affections f the nasal mucosa much more plausibly and without fewer contradictions than d the traditional theories.

RÉSUMÉ

Ces régulations se déroulent avant tout dans le système vasculaire et sont déclenchées par des irritations neuro-végétatives. Le principe des régulations est

expliqué les anastomoses artéro-véneuses dirigées par le système neuro-végétatif étant considérées comme des facteurs effecteurs. Dans ce domaine, l'hypoxie tissulaire accompagnée d infiltrations lymphoplasmo-cellulaires joue un rôle particulier

ZUSAMMENFASSUNG

Diese Regulationen spielen sich vorwiegend im Gefässsystem ab und werden durch vegetativ-nervöse Irritationen ausgelöst Das Regulationsprinzip wird er klärt wobei als effektorische Anteile die nervös gesteuerten arteriovenösen Anastomosen angesehen werden Dabei spielt die Gewebshypoxie gemeinsam mit den lymphozytär plasmazellulären Infiltraten eine besondere Rolle

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STUDIES OF ETIOLOGY OF LARYNGEAL PAPILLOMA AND AN AUTOGENOUS LARYNGEAL PAPILLOMA VACCINE

P H HOLINGER M D[1] N L. SHIPKOWITZ, Ph.D[2] J C. HOLPER Ph D[3] and M C. WORLAND, M.S.[4]

1 Electron microscopic studies have f iled t demonstrate virus par ticles in papillomas of four patients with laryngeal papilloma and one patient from whom the entire base of the papilloma was exuised and ex ised from the tracheal wall.
2. No growth was obtained at the sit of inoculation of the larynx of three female Rhesus monkeys whose true and false cords were inoculated unilaterally with 0.5 ml of a suspension mad from papilloma removed from two children and one adult.
3. It was ot possible t duplicate work reported previously which had indicated the presence f a species-specific virus capable of producing growth of tissue cultures with regrowth after blind serial tissue culture passes.
4 Blood samples were collected before and after vaccin therapy in patients w th lary geal papillomas so that in case a virus was isolated the viral agent could be used as the antigen in a serological reaction nce the virus could not be isolated, there could be no serological evaluation of cine therapy
5 The preparation and administration of an autogenous laryngeal papilloma accin is described with th results of this therapy a used in 1 patients.
6 Clinical evaluation showed that 28, or 55 per cent, were improved 12, or 23 per cent, were co sidered unchanged nd three or six per cent, deteriorated Inadequate information wa bt ined f seven or 14 per cent.
7 The annual operation rat calculated for 37 patients who had adequat data before and after operation showed that the annual pera tion rat decreased in 29 pati nt (78 per cent), did not ha ge in three patient (eight per cent) and increased slightly in five patients (13 per cent) Th nnual perat on rat before vacci e therapy was 4.00 after therapy was 1.88, an average of 2.12 perations per year

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An increasing amount of information concerning the etiology pathogenesis and clinical course of laryngeal papilloma is becoming available Yet this serious entity debilitating in many ways and occasionally terminating fatally still presents intriguing aspects that often seem quite incongruous Its species specificity and even its organ specificity have been established The difference in the clinical appearance of the lesions in children and adults, in spite of having an identical histological picture is another of the incongruities The influence of pregnancy stresses the hormonal component which has been a well established feature of the clinical course of the disease

Factors inherent in the site of this variant of a common dermatologic condition have widespread influence on respiratory and communication function and ability Not the least of these are the psychic trauma associated with a peculiar voice or a permanent or even temporary tracheostomy in a child or adult

Experimental work relating to etiology and the multiplicity of therapeutic procedures that have been used in an attempt to effectively treat or influence the growths have been reviewed in a previous publication (Holinger *et al.*, 1962) A number of additional avenues of investigation have been explored which might have bearing on the basic nature of laryngeal papilloma These are recorded in an effort to shed further light on problems of laryngeal papilloma Some of the results are essentially negative yet they contribute incidental information others are of a more positive nature and will be given in more detail

Electron microscopy

The tissues from four patients who had laryngeal papillomas surgically removed were studied with the electron microscope Ultra thin sections and negative staining were employed but no virus particles could be demonstrated. It was felt that since direct laryngoscopy and forceps removal of the papilloma was the choice method of surgery a truly complete removal of tissue was not possible In all probability the base of the tumor would need to be examined in order to demonstrate virus particles with the electron microscope The only possible way to obtain a block of tissue in which the *architecture of the papilloma and its centerlying structure were undisturbed would be to obtain a post mortem sample*

On November 15 1963 a four year-old boy (M B) was admitted to Chicago's Children's Memorial Hospital because of extensive and rapidly recurring papillomatosis. A tracheostomy had been performed previously because of respiratory obstruction At laryngoscopy and lower bronchoscopy it was found that the patient had papillomas above and below the tracheostomy tube the growth extending to the carina During the last of several endoscopic operations which had been only partially successful in clearing the trachea, a small hemostat was inserted into the tracheal open

ing and a large, intact papilloma with its stalk was "delivered" through the stoma and freed from the tracheal wall with a scalpel

The removal of this complete papilloma directly from the trachea resulted in a specimen that was undisturbed and especially suitable for study with the electron microscope. The tissue was fixed, and when ultra-thin sections were examined, no viral particles could be demonstrated.

Animal transmission studies

On May 8, 1964 at The Children's Memorial Hospital, papilloma were removed from the laryngees of two children. The tissue was triturated with a small amount of normal saline In addition, the stored, frozen laryngeal papilloma of an adult male with recurring papillomatosis was triturated in an identical manner Three mature female Rhesus monkeys were anesthetized with an intraperitoneal injection of Nembutal When deep anesthesia was obtained, with the use of a laryngoscope the left true and false vocal cord of each monkey were inoculated with a total of 0.5 ml of a papilloma suspension The right cords of the animals served as controls. The Brubaker Holinger endoscopic color camera was used to record the procedure

After one year the animals w re sacrificed There was no gross evidence of a papilloma at the site of inoculation. When the larynx was fixed and the site of inoculation examined microscopically no abnormalities were observed

Tissue culture studies

During the past five years, a sample of each laryngeal papilloma that was submitted for vaccine production was ground in m rtar and an aliquot of the suspension was inoculated into tissue culture tubes. Three blind serial tissue culture passes were made for each papilloma suspension. It was not possible to demonstrate tissue culture cytopathology or evidence of viral proliferation In these studies, it has not been possible to duplicate the work reported previously of producing growth of tissue cultures with regrowth on as many as eight passages (Holinger *et al.*, 1962)

Serology

Blood samples were collected from a number of patients before the start of autogenous papilloma vaccin therapy and then gain after the administration f the vaccine was completed. It was postulated that if a virus could be isolated from the laryngeal papillon a, it would then be possible to use thi viral agent as the antigen in a serological reaction. Since a virus could not be isolated, the serological evaluation of accine therapy could n t be completed.

Autogenous laryngeal papilloma vaccine

A resumé of the effect of an autogenous vaccine used during the past five years in the treatment of papilloma of the larynx is presented in a current publication (Shipkowitz *et al.*, 1967). This is a continuation of the previous study and relates to further analyses of the clinical material. The effect of this therapy has been evaluated by the patient response to the vaccine and the comparison of the annual operation rates before and after the use of the vaccine in a series of 51 patients. Of the 51 patients, there were 31 males, 20 females; three were Negro, one Mongolian, and 47 Caucasian. Sixty-eight per cent were under 10 years of age, 31 per cent had required at least one tracheostomy and in 16 per cent the papillomas had extended into the pharynx or the tracheobronchial tree. The duration of the condition prior to the start of vaccine therapy ranged from one to 391 months, with a median of 20 months. Histologic confirmation of the diagnosis was obtained in all cases.

The preparation and administration of the autogenous laryngeal papilloma vaccine has been as follows.

Fresh papilloma tissue was removed from the patient and placed immediately in sterile saline for storage at 4 C until the vaccine was prepared. Approximately 0.5 g of tissue was washed with sterile saline, minced fine with scissors and ground to a paste in a sterile mortar and pestle. The homogenate was suspended in 20 ml of sterile saline containing 1–1000 formalin. The resulting vaccine was incubated at 37 C for 24 hours and then tested for sterility by adding 0.5 ml of vaccine to two 10-ml tubes of thioglycollate broth and to one 10-ml tube of Sabouraud's broth. The broth tubes were incubated for 10 days: the Sabouraud's at 24 C, one thioglycollate tube at 37 C, and the second at 30 C. Sterile vaccine was then stored in a rubber stoppered vial at 4 C until used.

Each patient was inoculated intracutaneously with 0.25 ml of the vaccine thus prepared from his own papilloma and observed for any untoward reactions. If none occurred, the patient was injected with 0.5 ml of the vaccine subcutaneously. One week later the injection was repeated at a dosage of 1.0 ml. Vaccination was repeated each week thereafter at the 1.0 ml level until the vaccine was exhausted. When vaccine was administered to infants and small children, the standard dosage was reduced by 50 per cent.

The amount of vaccine used on any one individual varied from six to 65 injections with a median of approximately 18 injections depending on response and availability of the vaccine. Adverse effects were reported in six of the patients (12 per cent): in two of these the reaction consisted of no more than local discomfort at the site of injection; a rash followed an injection in one; mild local induration with transient ankle edema was observed in one; and localized inflammation and moderate lymphadenopathy in a fifth. The sixth patient developed atelectasis of the right lower

and middle lobe bronchi after previously having papilloma of the pharynx, larynx and trachea. The extension of the process into the bronchus was considered reason to discontinue the vaccine therapy by the referring physician, although such extension was well within the usual clinical course of this condition

RESULTS

The results of therapy have been assessed by two methods (*a*) the clinical evaluation of the patients overall response to the vaccine and (*b*) a comparison of the annual operation rates before and after initiating therapy From a clinical evaluation of the 51 patients in this series, 28 or 55 per cent, were improved after vaccine therapy 13 or 25 per cent, were considered unchanged and three, or six per cent, deteriorated during the course of the therapy or following it Inadequate information for proper evaluation was obtained in seven or 14 per cent.

The change in the annual operation rate after a course of vaccine therapy could be calculated for only 37 of the 51 patients because, in some, complete data for calculating change in annual operation rate after receipt of vaccine therapy were not available In others, vaccine was prepared from the papillomas removed at the first operation when the diagnosis was established which precluded comparative before-and-after calculations. Change in annual operation rate after vaccine therapy as calculated for the 37 patients for whom adequate data were available showed that the rate decreased in 29 patients (78 per cent) did not change in three patients (eight per cent) and increased slightly in five patients (13 per cent) Before start of vaccine therapy the mean annual operation rate for the 37 patients was 4 00 after receipt of vaccine therapy it dropped to 1.88, an average decrease of 2 12 operations per year Statistical analysis showed that the probability of obtaining such a decrease by chance alone is less than one in 1000

RÉSUMÉ

L étude préalable d'un vaccin utogè contre le papillome laryngé a été n r hie par l'analyse d'un plus gra d nombre de malades observés pendant plus longtemps. Des résultats favorables ont été obtenus comme l ont prouvé les réac tion des malades et la fréquence annuelle des opération vant et après le traitement pa le vacci Les données cliniques de cett étude seront présentées et évaluées.

ZUSAMMENFASSUNG

Ein früherer vorläufiger Beri ht über ein utogene Laryn Papillom-V kzine wird erw itert u d schliesst usät liche Patienten und ine längere Beobachtungszeit in Günstige Resultat wurden erzi lt und werden durch eine

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The amount of vaccine used on any one individual varied from six to 65 injections with a median of approximately 18 injections depending on response and availability of the vaccine Adverse effects were reported in six of the patients (12 per cent) In two of these the reaction consisted of no more than local discomfort at the site of injection a rash followed an injection in one mild local induration with transient ankle edema was observed in one and localized inflammation and moderate lymphadenopathy in a fifth The sixth patient developed atelectasis of the right lower

fact that papilloma is a species-specific type of path logy Thi is further apparent in experimental attempts t transfer papilloma between animal species, most f which are unsuccessful, with a few outstanding exceptions.

I appreciate Mr *Friedmann* confirmation that h too has been unable to identify virus particles in lectronmicroscopy studies.

M *A gell James'* w rk in ultrasound is most important, and his question in regard to th geographical distribution f papilloma is one of our on-going projects. Questionnaires have been sent t ot laryngologists in the Americas in an effort t help determin this distribution, but this work, s yet, has not been completed. We did find an unusual number reported from Haiti, which is imilar to the findings of Mr Angell James in regard to Thailand

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Regarding Mr B rk question of administration f vaccine i pregnancy we have not administered vaccine during pregnancy

Bewertung sowohl der Reaktion des Patienten als auch im Vergleich zu der jähr lichen Operationsfrequenz vor und nach Vakzinentherapie beurteilt Klinische Statistiken über dieses Stadium werden gezeigt und bewertet

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P H Holinger M.D Dept of Otolaryng logy
Univ rsity of Illin is Colleg of Medicine
Chicago Ill U.S.A

DISCUSSION

J E Bordley First I wish to congratulate the essayist on his presentation The fact that Mr Holinger was unable to reproduce the juvenile papilloma in the monkey vocal cord brings up the possibility that the tumor is specific for homo-sapiens

It is of interest that a number of members of the pathology department at the Johns Hopkins Hospital some years ago obtained a sterile specimen of juvenile papilloma at the time of instrumental removal at laryngoscopy and immediately implanted it in a small incision in the skin on the upper portion of the forearm in an area free from hair

The tissue lived and grew slowly for a number of years, at least six years, to my knowledge It was still growing at the time the host moved to another uni versity Light microscopic studies of the tissue after several years growth showed it to be in the pathologist s opinion identical to a juvenile papilloma

No attempt was made to carry out further transplants

I Friedmann I beg to confirm that electromicroscopy of several cases failed to reveal a virus or virus like particle One case of the late Professor Ormerod has had at least 14 biopsies studied with entirely negati e results

J Angell James Has Mr Holinger any information about the geographical distribution of papilloma? I was interested in the possible use of ultras und but found very few cases in the southwest of England When visiting Thailand I was told that the disease is relatively common and 30 new cases are seen annu ally in Dr Corns clinic in the University H spital in Bangkok

L. Rüedi How long do the improvements last after va cine therapy?

M Barretto Barretto Predo my former associate in S Paulo has given a previous report on the effect of smallpox vaccination in cases of pap llomato is. The results are very similar to those of Mr Holinger I should like to ask h m f he has done any experiment with other non specific viral vaccines

W P Work Do you recommend the use of this autogenous vaccine during pregnancy?

P H Holinger (Reply) The contribution of Mr *Bordley* confirms again the

fact that papilloma is a species-specific type of pathology. This is further apparent in experimental attempts to transfer papilloma between animal species, most of which are unsuccessful, with a few outstanding exceptions.

I appreciate Mr *Friedmann's* confirmation that he too has been unable to identify virus particles in electromicroscopy studies.

Mr *Angell James'* work in ultrasound is most important, and his question in regard to the geographical distribution of papilloma is one of our on-going projects. Questionnaires have been sent to otolaryngologists in the Americas in an effort to help determine this distribution but this work, as yet, has not been completed. We did find an unusual number reported from Haiti, which is similar to the findings of Mr Angell James in regard to Thailand.

Mr *Ruedi's* question of duration of improvement is difficult to answer because all cases treated since 1960 are included in the study which was terminated about two years ago, so that the results are those of a period of about five years.

Mr *Barrett's* remarks of the effect of non-specific smallpox vaccine are of interest. It is our feeling that this is a species-specific problem, in agreement with finding no effect on the growth by treatment of human papilloma with bovine papilloma vaccine.

Regarding Mr *Burk's* question of administration of vaccine in pregnancy, we have not administered vaccine during pregnancy.

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COMPUTATION OF THE NYSTAGMOGRAM

N. TOROK, M.D. and A. J. DERBYSHIRE, Ph.D.

From the Department of Otolaryngology, University of Illinois Medical Center and the Illinois Eye and Ear Infirmary, Chicago, Ill., U.S.A.

To study the interaction of the slow and fast component of the caloric nystagmus the total velocity of the slow components were plotted against time. The individual quick components were added similarly into a continuous curve. Whereas increased stimulations create increased slow phase velocity, the fast component speed remains constant. Graded caloric stimuli alter with similar proportions the slow component speed as well as the frequency count at the culmination. Incongruence of these two phenomena as well as traces on cathode ray oscilloscopes, indicates certain independence of the two phases of the vestibular nystagmus. Further evidence has been provided that both of these parameters, frequency count and slow phase velocity, are the best available expression of vestibular sensitivity.

Clinical neurootology is concerned with and predominately based upon the phenomenon of reactive or spontaneous vestibular nystagmus. The assessment of function and sensitivity of the vestibular apparatus is restricted mainly to the observation of this phenomenon. It became evident that prevention of fixation provides better observation. Alertness and elimination of undue light, sound or other distractions also were essential for reliable evaluation. Finally nystagmography fulfilled various desirable objectives for assessing these eye-movements. The photoelectric technique, in particular, may amplify the nystagmus to any desired magnitude. The records are available for detailed and specific studies, and so without exaggeration, the recording of nystagmus has reached a close to perfect level. These improvements enabled the evaluation of several parameters of the response. The velocity of the slow phase was found to be a characteristic feature, the frequency count per time unit proved to express specifically the sensitivity of function. These were great improvements over the past and gave greater security to the neurootologist at the time of these discoveries.

Standard stimulation and recording of the provoked vestibulocular reflexes in healthy individuals provided the information necessary for establishing what may be considered as normal. Thus a reference became

This study was supported in part by U.S.P.H.S. NIH Research Grant NB-1711

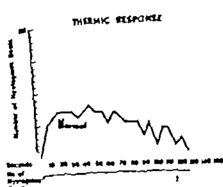


Fig. 1

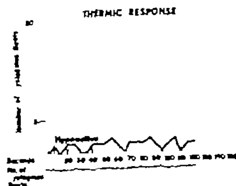


Fig. 2

Fig. 1 Normal postcaloric nystagmogram The frequency of the postcaloric nystagmus is plotted on co-ordinate system. The lacinae marked 1 5 sec time units serves the time scale for the duration of the nystagmus response The ordinate represent the nystagmus frequency The line of digits below the nystagmogram indicates the number of nystagmus beats in every 5 sec The culmination 1 7 and 8 for two consecutive 5 sec time unit which makes 15 for the 10 sec at the peak of the response.

Fig. 2. Hypoactive postcaloric nystagmogram The duration of this response does not differ from that of the normal caloric reaction. There is marked reduction in the nystagmus frequency i.e. intensity It is flat curve The maximum frequency or culmination for 10 sec is 3. A acoustic tumor was diagnosed and successfully operated on.

available to discriminate between physiological and pathological, i.e., normal and diseased

Since it is easy to differentiate individuals with normal hearing from those with defective hearing on the basis of the pure tone audiogram it was logically expected to identify the normal and abnormal vestibular reflex responses.

By plotting the frequency of the postcaloric nystagmus on a coordinate system, the average normal (Fig 1) can be readily distinguished from the pathological, which may be either below (i.e. hypoactive) or above (hyperactive) the limit of responses obtained in normal subjects.

The decreased response is variably termed as hypoactive reaction, decreased sensitivity vestibular paresis, etc (Fig 2) Such a finding is accepted as objective evidence of a lesion The localization or site of the pathology is not immediately defined Other clinical data and an integration of such findings with all the available vestibular and cochlear responses should facilitate the topical diagnosis.

The increased response (Fig 3) The term hypersensitivity is incorrectly applied to these responses. There is no increase in sensitivity above the normal level in sensory organ physiology Instead the provoked nystagmus as a reflex response is exaggerated. This neuropathological phenomenon is similar to the increased tendon reflex indicating a lesion of the pyramidal

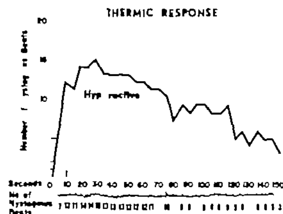


Fig 3

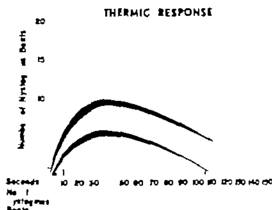


Fig 4

Fig. 3 Hyperactive postcaloric nystagmogram The nystagmus frequency is increased considerably right at the onset The culmination reaches 14 and 16 beats in the peak two consecutive 5 sec period So the culmination is 29 far above the average normal This increased vestibular response indicates a central lesion A meningioma in the middle cranial fossa was diagnosed

Fig. 4 The normal range of the nystagmus frequency and particularly the culmination within the normal range is indicated by the shading Identification of the abnormal becomes evident whenever it is below or above the shaded area

system produced by some defective inhibitory mechanism Such a nystagmus finding may not be a vestibular abnormality per se, but rather a lesion of the inhibitory mechanism in the nystagmus pathways It can be postulated with certainty that an increased nystagmic response is a sign of central nervous system pathology More specific meaning arises when such *a finding is unilateral*

The study of the frequency of the provoked thermic or rotatory nystagmus thus facilitates a fairly clear discrimination between normal and abnormal (Fig 4) For any practical purpose the clinician can depend upon the culmination value and frequency behavior of the nystagmus sequence

We have advanced considerably in vestibular function evaluation since the time when the nystagmus duration was checked with a stop watch With all the improvements and refinements in technique and evaluation principles, it would be an overstatement to say however that we have arrived at a fully satisfactory answer Most confusing may be the wide variations of responses in normals Overlapping responses between findings considered as normal and abnormal creates uncertainties The search for more clues in the nystagmus record must therefore be pursued

In our present study instead of concentration upon nystagmic details the interaction of the slow and rapid components were analyzed The intriguing composition of the two components created problems and controversies for almost a century The prevalence of the slow phase as the primary vestibular reflex is generally accepted The role and significance of

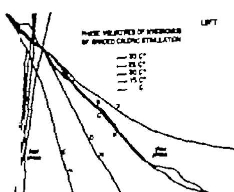


Fig. 5.

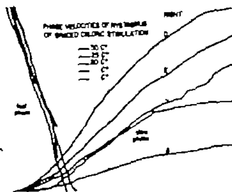


Fig. 6

Fig. 5. Graded stimulation response of the left horizontal canal The slow and f st component peed of the lorie yst gmus are summed. The fi curves of th slow phase locity represents the effects of the fi graded stimulation. (A: 30 C, B 25°C, C. 20°C, D 15 C, E 10°C of 100 cc of w ter) While the low component peed gradually ncreases with the stronger stimulation, the fast compo nt peed rem ins ncha ged. The number ne each slow phase curv l the respecti maximum frequency per 10 sec (culmination lines)

Fig. 6. Graded stimulatio respo se for the right horizontal canal

the rapid component, however is not settled satisfactorily It is assumed to be a compensatory phenomenon. The anatomical origin and neural path ways controlling the fast phase are not fully understood

In our investigations, the following procedure was carried out rotatory and thermic nystagmograms were obtained from normal healthy indivi duals by using the photoelectric (PENG) principles. A series of graded stimulations were applied Although both rotatory and caloric stimulations were performed, this report will describe only the caloric responses. Each ubject received five pairs f caloric stimulations. For the first pair of tests 30 C water was used (100 cc in 20 seconds with the head in the optimal position, i.e 60 back from the upright) The consecutive stimulation contained 25 20 15 and 10 C water A minimum of five minutes waiting period between the two stimulation was maintained care was taken that all the testing procedures were executed in a standard manner

The nystagmograms were analyzed by summing all slow components along each individual response keeping their relative time relationships (Fig. 5) The slope of this curve at any point expresses the velocity of the low phase at that m ment. The individual fa t component velocities were also summed. This comparison of all slow phases again t all rapid component creates one giant nystagmus with the speed, time and direction of m tion represented (Fig. 6)

On ne chart the response to all fiv graded stimuli are plotted. The five ny tagmu patterns clearly show the nature of this vestibular reflex. To

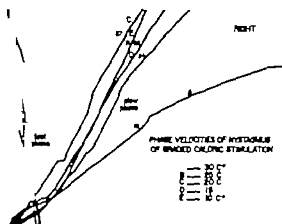


FIG. 7 Irregular slow phase velocity response to graded stimulation. The velocity following 20 C stimulus is faster than the slow phase speed of 15 C and 10 C stimulations. The culmination values are proportional.

present all the characteristics of the response the maximum frequency at the peak of the reaction i e the nystagmus culmination was also counted.

As expected, the increased stimulation strength resulted in an increasing response of slow phase velocity and maximum frequency count. The most striking fact is that while the slow phase velocity is increased with more or less regularity and proportion the velocity of the rapid phase remains conspicuously identical regardless of stimulus strength. On the other hand the maximum frequency count of the fast phase changes proportionately with the degree/sec of the slow phase curve.

The range of increased response most frequently was gradual but the magnitude of the increase could differ (Fig 7). The slow phase velocity ranged between 12 /sec for 30 C water to 32 /sec for 10 C water whereas another subject exhibited a 30 /sec through 39 41 66 to 80 /sec gradation for the same stimulation series. The frequency culmination similarly (Fig 8) varies between 10 beats per 10 sec in the first mentioned case for 30 C water and 23 beats at culmination for 10 C stimulation. In the second mentioned subject the frequency increased gradually for 13 beats to 18 21 32, and to 41 beats for 10 C temperatured water.

The mathematical relation between stimulus strength and response can approximate linearity. The majority of our subjects did follow such a rule. Anomalous findings did occur in some instances, however when one stimulus response out of the five was disproportional to the rest (Fig 9).

There is no clear explanation to the anomalies. They do occasionally occur and it is familiar for all those involved in regular vestibular testing. A number of factors have been mentioned as reasons for such discordance. Mental distraction either by undue nonspecific stimulation or diminution of activity such as drowsiness or mental excitement are considered as common causes. This discrepancy occurred in the measurement of slow phase velocity just as well as in frequency culmination. It is noteworthy that an

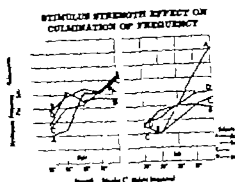


FIG. 8.

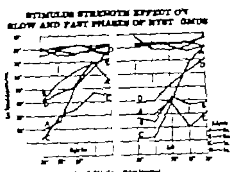


FIG 9

FIG. 8. The culminati ... lue shows pproximat linearity with the stimulus strength. The range of increase i mostly gradual, but the magnitude of increase differs (compare D nd A curv on the left side)

FIG. 9 The slow phase locity increases according t the stimulus strength The alues of speed spread over wider scale than those f the frequency culmination

incongruity of one single response never affected the slow phase velocity and frequency maximum at the same time This observation was unex pected and contradicts a direct interrelation of the two phenomena.

Our findings support and confirm our previous assumption and clinical experience that the frequency of the evoked nystagmus is an adequate measure of intensity of the reflex.

By studying the slow and fast component interchange, it was possible to photograph a series of consecuti e nystagmus beats on the oscilloscope with superimposing eight nystagmus on the screen (Fig 10) In spite of the identical slow component speeds, the fast phase appeared at different time intervals. Furthermore, by studying individual fast phase appearances, (Fig. 11) it is sometimes evident that the slow phase has no constant veloc ity and the fast phase may occur not at the height of the slow phase speed, but after some decrease of the slow phase velocity

It becomes questionable therefore whether the frequency depends upon the slow component speed. The slow phase velocity is a direct vestibular reflex however it is possible that the fast component may also be a direct vestibul r response The slow phase velocity and the frequency of the fast phase are hanging congru usly and proportionally to the stimulus strength. This relation was studied statistically with the culmination count as the dependent variable and the maximum slope of the slow phase velocity as the independent ariable The slope of the regression was 0.32, indicating a proportionally greater sensitivity of the culmination count, than of the slow phase velocity The correlation (Pearson r) equ ls 0.83 with a correlation coefficient of 0.69 This i evidence of a strong relationship, so that 0 of the variation of the culmination count can be predicted from the

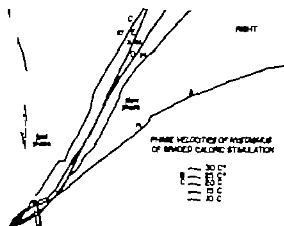


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Wechselwirkung dieser beiden Vorgänge zu gewinn n. Die Ergebnisse der Ana lysen und die Hypothesen die ihnen unterliegen sowohl als die sich daraus ergebenden weiteren Folgerungen werden besprochen.

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(Medical Cent and the Illinoi Eye nd
Ear Infirmary Chicago, Ill U.S.A

DISCUSSION

H Arslan The problem exposed by Mr Torok, that is the observed (with computer work) correlations between the slow and quick phase f nystagmus, can f d a physi logical e planation in the dep nd nce existi g between "in ten ity f the afferent vestibular e citation and the "intensity of the response of th reticula and secondary vestibular pathways, whi h elaborat the qui k phase of n st gmus.

H Davi By the term culmi ation of frequency" do you mean the peak frequen y f llowing the timulation?

A mod l for the relation between th slow and fast components is suggested by the discharge of impulses in auditory nerv fibers. The fast compon nt ma be triggered by the slow component after an interval that is directly related to the slope of the slow component on which is superimposed a random process. I hope th t such model will pro useful.

C R Pfalt I should l ke t confirm M Torok s opinion that the maximum response f llowing thermic stim lation of the labyrinth—i.e the culmination period of e lort n stagmus—i rather important param ter with respect to the valuation f thermic nystagmus. Dr Torok has shown a particular type of culm tion which he calls hyperacti e type According to our own bserva tions, th pathological increase f nystagmus int nsity i always symptom of central estibula lesion. We found it more frequently in cortical or subcortical lesion of the central ervou system than in lowe brain stem lesion and hen assumed thi particula pattern of th calori response to be symptom f supratentorial vestibula lesion. I should lik t ask Mr Torok if he may confirm our previous observations by hi own fi dings.

G Dohlman The correlation between the peed of the slow phase nd th triggeri g of th f st phase is in my perience xposed t so many variables that t is diff cult for me to see clear corr lati As an example I would like t mention an experiment I recently h d the opportunity to learn about in D Henrik son laboratory in Lund. H was able t show that nicotine from smok



Fig 10

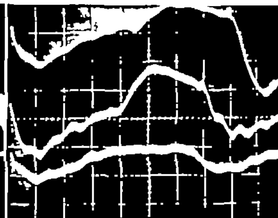


Fig 11

Fig. 10 Supe impositi n of 8 nyst gmic be ts (triggered by v ltag of fast phase 1 cm = 0 1 sec, amplitud gain constant) Note the lopes of slow ph ses are uperimposed and consist nt while the fast phase ubsequ nt t th t igg ring is scattered.

Fig 11 Three individual sweeps, ea h t iggered by a fast phase (1 cm = 0 1 sec and amplitud gain constant) Not that ubsequent f st phas appears after ma imum of slow phase is reached (e en at a decrease from maximum in one sweep)

slope of the slow phase velocity There is less than one possibility in 100 000 that such a relationship could be found as a result of chance.

These observations and principles form an adequate basis on which we are developing a program for electronic computation of the nystagmogram Our nystagmic data are recorded in the conventional manner but transfer red simultaneously on an FM magnetic tape which provide the information to the computer Immediate calculation of the slow phase velocity integrated with a continuous frequency count is expected to provide further specified and prompt answers to measure and assess vestibular sensitivity

ACKNOWLEDGMENT

The authors wish to express appreciation to Miss Linda Poznanski B.A for her valuable assistance in testing reading the nystagmograms and charting the records

RÉSUMÉ

Le paradigme que nous utilisons pour analyser le nystagmogramme essaie non seulement de mesurer chacun des deux constituants individuels du ny tagmus mais aussi d exprimer leur interaction Les résultats de ces analyses, le hypothèses et les implications qui en découlent seront discutés.

ZUSAMMENFASSUNG

In unserer Analyse des Nystagmogramms versuchen wir nicht nur lie Werte beider Nystagmuskomponenten zu bestimmen sondern auch eine Finsicht in lie

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AVERAGED-EVOKED-RESPONSE EEG AUDIOMETRY IN NORTH AMERICA

H. DAVIS, M.D.

From the Central Instit te for the Deaf St. Louis M U.S.A.

Averaged evoked responses recorded from the vertex (V potentials) are a aled ba is for "physiological audiometry" In infants and young children Th ir responses are slower and more variable than in older children and ad lts. A response t t ctile stimulation is useful guide to the form f the a ditory pattern if the auditory threshold is high Good agreeme t among the eight or ten most active laborat ries in N rth America ha been reached on th desirable parameters of stimulation nd recording. The values are summarized and references are given to significant recent publication from each laboratory

In 1964 in Würzburg we described the slow cortical responses, which we now call the vertex or "V" potentials, that are evoked by auditory tactile and visual stimuli, and we reported our first experiences in their use as an endpoint for what I now like to call "physiological audiometry" (Davis, 1965) Since that time both we at Central Institute for the Deaf and our colleagues in other laboratories in the USA and Canada have con tinued to study them One approach relates them to the maturation of the nervous system in infancy (Engel, 1967 Ellingson, 1964) Another approach relates them to the depth of sleep (Williams *et al* 1964 Goff *et al* 1966) Another is concerned with modifications related to neurological abnor malities (Rapin *et al* 1966 Barnet & Lodge 1966) Others study their physiology (Cody & Bickford, 1965 Davis, 1966 Rapin *et al* 1966) and still others (who are not included in our list of references) their relation to the tat of the subject his expectations and the amount of information he recei es On the whole the photic responses are more popular than auditory largely because the early response of the primary projection area of the visual cortex can be recorded and tudied.

Most of those interested in the audiometric use of V potentials have studied leeping infants or young children, using a sedative such as chloral hydrate when necessary (Appleby 1965 McCandless & Best, 1966 Price *t al* 1966) The Central Institute for the Deaf however is not a medical institution We therefore never use a drug but have tried to adapt our tech

This in estigation w supported by Public Health Service Research Grant N B-3856 from the National Instit t of Neurological Diseases nd Bli dness.

ing dramatically changed the correlation between slow and rapid phase The speed of the slow phase remained unchanged whereas the rapid phase became more pregnant and the speed of the rapid phase was decreased Presumably this refers to the influence of nicotine on the reticular system as one of the sources of influences on the correlation between the two phases

L B W Jongkees As regards the stimulation used in these experiments I want to point to the fact that the caloric stimuli is very impure and cannot very well be used for quantitatively experiments. I hope that Mr Torok and Mr Derbyshire will repeat their experiments with a purer form of stimulation like e.g rotatory acceleration It is very good that the authors brought forward again the extreme importance of the wide variations of the vestibular reactions in normals.

N Torok (Reply)

to Mr *Arslan* Essentially offered further explanations to our assumption It is possible indeed that contrary to our long established concept the fast nystagmus component is more dependent upon direct vestibular effect than on the velocity of the slow phase

to Mr *Davis* The term "culmination" is a commonly used expression in vestibular terminology It refers to the maximum or peak intensity of the post caloric nystagmus. The suggestion of a model to be constructed in order to better explain the slow and fast phase relationship was already conceived by us. Dr Davis advice will certainly encourage us in our further efforts to clarify the origin of the fast component

to Mr *Pfall* The hyperactive vestibular responses must be considered pathological and of central origin The mechanism causing this phenomenon might be explained by an example from neuropathology Increased tendon reflex indicates some pyramidal lesion where the inhibitory mechanism in the reflex arch is damaged The increased nystagmic response can be caused by a lesion to the inhibitory mechanism within the nystagmus pathways. Such a lesion might not be a direct vestibular defect and can be located within the eye muscle coordination system The vestibular stimulation then evokes an uninhibited oculomotor system resulting in an increased nystagmic response

to Mr Dohlman The experiment mentioned by Mr Dohlman serves as support to our contention Cigarette smoking irritates perhaps the central vestibular apparatus in a special form where the slow phase remains unaffected but the central source or origin of the fast component responses with an increased reaction

to Mr *Jongkees* who terms the caloric test "dangerous" It was mentioned earlier that in our study graded rotatory stimulation had been executed along with graded caloric testing Because of time limitations our present report was restricted to the caloric responses. However until some better or improved testing or stimulating method becomes available we must depend upon the caloric stimulation

The use of "thermic instead of caloric" testing may be justified Barany invented the word "caloric more than 60 years ago What he really meant to define was the effect of heat upon the endolabyrinthine fluids. Calories are not involved in the reaction On the other hand in our weight conscious society the term "calories" has a specific meaning, certainly not applicable to the testing procedure of the vestibular receptors. "Thermic" is not a new term in this respect, but certainly a more appropriate expression than caloric"

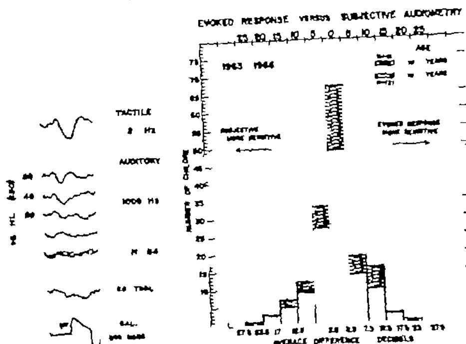


Fig 1 Fig. 2.

Fig. 1 Auditory and tactile responses of normal adult, showing the similarity of tactile and auditory responses and the presence of auditory response at 5 dB hearing level (ISO) (From Davis & Niemoeller *J Speech Hearing Disord rs*, in press, by permission.)

Fig. 2. Distribution of the differences between estimates of the physiological evoked-response thresholds and classical finger-response threshold for 102 children with impaired hearing (Central Institute for the Deaf. Each rectangle represents the average of the differences at 500, 1000 and 2000 Hz. The agreement is good for 1–6 years (crossed) as for 7–15 years of age (shaded). (From Davis, Hirsh, Shelnutt & Bowers, *J Speech Hearing Research*, in press, by permission.)

larger number of responses, but then the danger of a change of state increases.

The patterns of response of a given child are not completely variable, however. If they were we could not *extract an* "average" response from the background. There is still an individuality of pattern but it is not as clearly defined and reproducible as in an adult. On the other hand the *differences across children* may be so great that the waves seem to be in almost exactly opposite phase, positive versus negative. This makes it quite impractical to employ rigid rules, such as we *would like to write* in order to program a computer to recognize the positive patterns.

A very useful procedure for identifying a *small* response which only appears at stimulus levels near the upper limit of the audiometer is to record a response to *tactile* stimulation, and to superimpose this pattern

nique to the requirements of the restless and sometimes antagonistic young children most of them two to six years old who come to our hearing clinic for evaluation We have simplified and standardized both our procedure and our equipment and we hope that a commercial model built to our specifications by the Princeton Applied Research Corporation will be on the market at a reasonable price by the summer of 1968 We have been encouraged to proceed in this development by the excellent agreement among a number of the investigators named above who assembled in Los Angeles at the invitation of Drs Victor Goodhill and Edgar L. Lowell All agreed that the method held great promise for audiometric assessment of children suspected of auditory impairment in the difficult but important first three years of life The following details drawn from our own experience express, we believe the consensus of that group

First we can estimate with good accuracy the behavioral (or finger response) threshold of hearing in children of four years and older from their V potentials The V potential is an on-effect and its amplitude is not closely related to the loudness of the stimulus so that there is no necessity that the two thresholds, physiological and behavioral should coincide Fortunately the agreement is quite good, particularly when, as in our case the observers who estimate threshold from a set of V potential records by interpolation or by extrapolation, have the benefit of constant and immediate feed back from comparison of their estimates with subsequent behavioral tests. Fig 1 illustrates a series of (adult) auditory V potentials recorded with our simplified clinical evoked response audiometer We shall comment in a moment on the great value of a tactile response as a guide in cases where the auditory response is weak or absent Fig 2 shows the summary of our comparison of evoked response audiometry with classical behavioral "finger response" audiometry for all of the children at CID who had both measurable hearing and identifiable V potentials at frequencies 500 1000 and 2000 Hz. For the first two years we employed tone pips (filtered clicks) as stimuli, in the third year we substituted standard audiometric tone-bursts The agreement between the two methods was equally good The figure shows that age, at least for 4 years and older is not a significant factor Our estimates are neither better nor worse for those 4 to 6 years old than for those 7 through 16 years old

We have already reported (Davis, 1966) that the V potentials of children are more variable than those of adults. The variability is particularly troublesome for very young children It is not only that a young child particularly an infant, may suddenly fall asleep during a test or pass from light sleep to deep sleep The monitor EEG can at least give warning of such changes. Even with a constant background EEG pattern the latency as well as the amplitudes of particular waves may vary considerably from one trial to another The physiological "noise of the background EEG which is often semi rhythmic and of high voltage contributes an important part of this variability In principle it could be reduced by averaging a

Repetition rate, for waking subjects, 1 per sec sleeping, 1 every 2 sec. (This repetition rate gives the maximum voltage per minute but it is not critical.)

Number summed in a trial 50 to 64 Some workers prefer summing fewer responses at a slower rate

Duration of sample following each stimulus 500 msec (waking) or 1000 msec (sleeping)

Time constant of the EEG machine long enough to record 3-per-second delta waves without gross distortion or phase shift

With a skilful and experienced assistant to apply the electrodes and to amuse the child with toys, pictures, puppets, etc., we can usually obtain 20 or possibly 24 one minute stimulation periods, with one or two play periods interpolated, before the child becomes too restless. The total time is a little over an hour With a reasonably cooperative child and using on line strategy like the game of "20 questions we often obtain a five frequency audiogram for each ear in this time.

RESUME

Les réponses evoquées moyennes auditives recueillies sur le vert x (potentiels V) sont une base lable pour un audiométrie phy iologique chez le nour risson et hez le jeun enfant do t les réponses sont plus lentes et plus variables que celles du grand enfant et de l'adulte Une réponse à une stimulation tactile sert de référence pour déterminer la forme du pattern, lorsque le seuil auditif est levé Entre les huit ou dix plu importants laboratoires nord-américains, un xcellent accord est i tervenu pour fixer les meilleurs paramètres de stimulation et d'enregistrement dont les valeurs sont données. Pour haque laborat ire la plus cente et ignif cative publication est rapportée.

ZUSAMMENFASSUNG

Elektron sch ermittelt om Schelt l abgele tete „evoked responses (V Potentiale) stellen ine w hlbegründet Basis für ei phy i logische Audiometrie en Sa gl ngen und Kl inkindern d Die Reizantworten sind langsamer und ariabler l bei älteren Kindern und Erwachsenen Die A twort auf taktile Reize st in ulch her Anhaltspunkt fü d Beurteilung von Hörmustern bei erhöhter Hörschw lle Unter d n 8 oder 10 kinsten Laboratorien in Nordamerika konnte eine gut Übere stimmung über die wünschenswerten Stimulations- u d Registrierp rameter erz lt werden Diese Werte werden zusammengef st, und es wird of je ine neue bedeut nd Publikation der inzelnen Laborat rien hinge wiesen.

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The l q f references i confined t recent studies i U.S.A. d Canada of the few k potential i mu th t re particula l relevant t evoked-response audiometry

VERTEX POTENTIALS IN CHILDREN

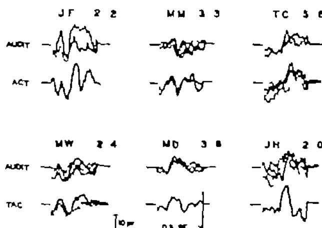


FIG. 3 Auditory and tactile V potentials of six young hard-of-hearing children The auditory responses were evoked by loud tone bursts of different frequencies. Note the *general similarity between auditory and auditory and between auditory and tactile for* the same child, and the considerable differences across children The latencies-to-peak in M.D (age 3 years 8 mo) are very unusual although not unique

on the unknown pattern on a trans illuminated surface The eye detects similarities of pattern very readily in this way even in the presence of considerable noise Of course if a large clear auditory response appears at a high stimulus level it can be used instead of a tactile response to identify small V potentials near threshold It should be remembered, however that the latency of a tactile response is some 20 to 30 msec longer than the auditory response and that very near threshold the latency following a tone burst may be significantly lengthened (Rapin *et al* 1966) Tactile responses can usually be recorded from young sleeping children without awakening them

Fig 3 illustrates the variability of V potential patterns among children and the similarity *for each child between his* auditory and *his tactile* responses. In several cases we have superimposed two or three average responses to indicate the variability due largely to "noise from one trial to another

The parameters of stimulation which were agreed upon as desirable for routine clinical evoked response audiometry and which we have incorporated in our design are as follows.

Auditory stimulus tone bursts from a standard audiometer calibrated to ISO scale with rise time between 20 and 30 msec. (Alternative transducers for infants are Sharpe earphones in circumaural cushions and a loudspeaker)

Tactile stimulus a vibrator like an oversized boneconduction vibrator applied to the palmar surface of the fingers. The hand lies, palm up on a pad of sponge rubber 125 Hz tone bursts from the bone-conduction output of the audiometer suitably amplified are appropriate.

H. Davis (Reply) The variability of the patterns follows two definable trends. The patterns are slower th younger the child and they are slower in sleep The greatest difficulty arises when the background EEG is of high voltage and that of the potential i small These are indi idual characteristics a d there is no necessary relation between the two We repeated the tests on the children with whom we mad th worst errors a d we tended to make the same errors on the second test. Th problem is to recover a small signal in a high le el of background n ise within a reasonabl time We make a compromise here.

We re investigating the possibility that certain variations in particular waves may reflect neurological abnormalities, but as yet we have no definite results to report.

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Th Central Institute fo th Deaf
St Loui M U.S.A

DISCUSSION

A J Derbyshire I wish to congratulate Mr Davis on his presentation of such strong data showing the precision of relation between behavioural and EEG auditory thresholds. Would he discuss the reasons why there are deviations from the central close relation? Are the deviations the result of changes of state or are there other factors such as those produced by specific types of auditory problems that could help in the understanding of deafness and improving diagnosis?

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ON ACOUSTIC RESEARCH AND ITS CLINICAL APPLICATION

J J ZWISLOCKI Sc.D
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Recent acoustic research employing improved instrumentation and rigorous analysis has led to a rather detailed understanding of the normal and pathological middle-ear function, and to a new diagnostic methodology This methodology complements the audiometry

INTRODUCTION

I was asked to review for you some of the recent acoustic research that has been going on in my laboratory at Syracuse University and to discuss some of its clinical applications Before I do so let me digress a little and point out to you a paradox in the examination of the ear that seems to have escaped notice The paradox concerns testing of the middle ear function

The middle ear transmits sound by means of minute, submicroscopic vibrations. These vibrations are the essence of its functioning and it is adapted to them It is not designed for large visible motions which are known to distort its normal mode of operation Neither is it designed to transmit light, as all those who have tried to see beyond the eardrum must know Yet, practically through the whole history of otology and audiology men have made strenuous efforts to avoid sound and small vibrations in the examination of the middle ear and to use light and large visible displacements. Audiometry which uses sound provides only an indirect test of *sound transmission and cannot be regarded as a direct examination* of the middle ear

The limitations of visual inspection and of hearing tests often leave the middle ear shrouded in a veil of diagnostic mystery

METHOD

We have attempted to fill the obvious gap in the methodology of ear examination by developing what we call an acoustic method The method takes as a point of departure the pioneering work of Dr Metz performed in the 1940s, and culminates in a clinical instrument and a table of acoustic symptomatology It is designed to complement the otoscopic examination and the hearing tests. It provides a check on the often uncertain results of bone conduction testing and permits a diagnostic differentiation among

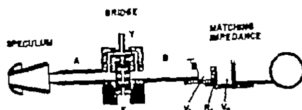


FIG. 1 Longitudinal section through the acoustic bridge drawn schematically. (From the *Journal of Speech and Hearing Research*.)

middle ear malfunctions. In addition, it allows otherwise unnoticeable small changes to be detected.

The method is based on a partial reflection of acoustic waves at the eardrum. This reflection depends not only on the state of the eardrum but also on that of the ossicular chain and the cochlear windows. Even the cochlea has an effect on it. Through acoustic measurements on normal and pathological ears and with the help of anatomy and acoustic theory we have been able to analyze the middle ear function in detail and to correlate the acoustic changes measured at the eardrum to middle ear pathologies. In a way we have learned to look acoustically beyond the eardrum

The reflection of sound waves at the eardrum depends on the effective resistance stiffness and mass of the middle and inner ear system. It should be noted that, in the technical language, resistance means only one force component specifically the one that results from friction. The latter arises in ligaments, muscles, and ossicular joints of the middle ear However the main acoustic resistance component of the ear stems from the wave motion in the cochlea, as has been demonstrated first theoretically and later experimentally It also should be mentioned that, in mechanical systems, the mass interacts with stiffness in a way that tends to reduce the effect of the latter and make the system appear more compliant. The effect is most pronounced at the resonance frequency where th system becomes infinitely compliant. In the normal ear the main resonance occurs somewhat above 1000 Hz.

The instrument we have developed for the acoustic examination of the ear is based on Schuster's principle of an acoustic bridge We have succeeded in designing it in such a way that it measures directly the effective acoustic resistance and compliance at the eardrum The first slide (Fig 1) shows its schematic drawing.

At th far left is a special speculum with a soft plastic flange It is designed to properly place and seal the bridge in the ear canal. The bridge itself contains two main tubes *A* and *B* which are symmetrical with respect t a central electroacoustic transducer *E* The transducer radiates sound waves into tubes *A* and *B* in phase opposition. The wave in tube *A* is partially reflected at the end of the tube and partially at the eardrum The wa e in tube *B* i reflected at the set of variable acoustic elements labeled

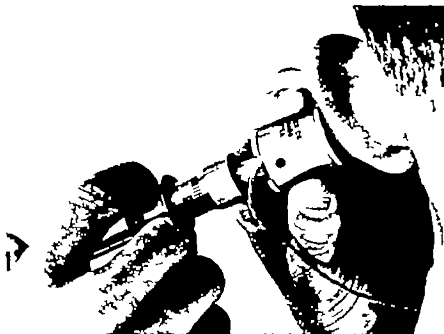


Fig 2. The acoustic bridge held in its operating position (From *International Audiology*)

matching impedance If the reflections in both tubes are equal the resulting sound waves cancel each other out in the middle of the small tube bridging the transducer Under these conditions, practically no sound can be detected in the output tube V

The set of variable acoustic elements consists of two volumes of air separated by a narrow slit The first volume V_1 simulates the ear canal and is adjusted to match the volume of each individual ear canal before the beginning of actual measurements. The volume is determined by filling the ear canal with alcohol with the help of a calibrated syringe The second volume, V_2, supplies the acoustic compliance which is matched to the effective compliance at the eardrum The narrow slit provides an acoustic resistance which can be made equal to the acoustic resistance at the eardrum The measurement is executed by varying the volume V_2 and the resistance R until the sound in tube V is minimized When this is achieved the effective compliance and resistance can be read directly on the bridge dials The variable compliance and resistance are mutually independent and can be adjusted within a minute or two

The next slide (Fig 2) shows how the instrument is held in the ear The black tube leads to the examiner's ears.

MIDDLE EAR FUNCTION

Let us now consider the functional anatomy of the middle ear which is shown in the following slide (Fig 3) In the normal ear the central por

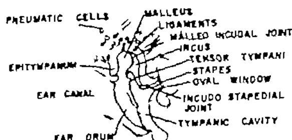


FIG. 3. F nctional nat my of the middl (From the *Jou nal of the Acoustical Society of Am rica.*)

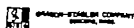
tion of the eardrum and the three ossicles vibrate nearly as one rigid body At frequencies below about 500 Hz, this motion is controlled mainly by the compliance of the ossicular attachments and of the membrane of the round window When the incudo-stapedial joint is severed the compliance measured at the eardrum is doubled When the stapes is fixed the compliance decreases to about one half of the normal value It does not go to zero because some relative motion occurs in the ossicular joints Between 500 and 1500 Hz, the effective compliance of the middle ear system is enhanced by the mass of the ossicles. Somewhat above 1000 Hz, the compliance tends t become infinite in th normal ear Ossicular separation brings the resonance point down to about 700 Hz. Stapes ankylosis shifts it toward higher frequencies.

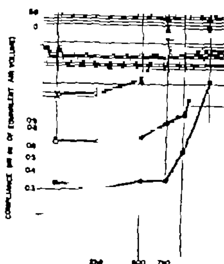
The effective resistance of the normal ear decreases somewhat from low to high frequencies. Ossicular separation reduces it at low frequencies to less than one half This is so because the main source of resistance, the cochlea, becomes disconnected. Stapedial ankylosis increases the resistance at low frequencies because of friction in the ossicular joints.

The greatest reduction in compliance at the eardrum occurs in the presence of massive adhesions to the malleus, since the malleolar umbo becomes immobilized and the only possible motion is confined to the peripheral portions of the eardrum. Under these conditions, the effective resistance tends to be very high.

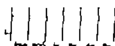
RESULTS OF ACOUSTIC MEASUREMENTS

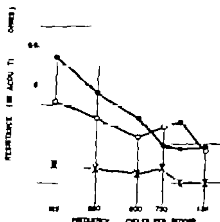
The next slide (Fig 4) shows median compliance and resistance values f normal and otosclerotic ears as well as of ears with ossicular separation. The compliance is plotted in terms of an equivalent volume of air (V_2) the resistance in acoustic Ohms—but the absolute values do n t interest us here It i clearly evident that otosclerosis leads to a substantially reduced compliance and ossicular separation to a substantially increased compli











O NORMAL (33 E)

● OTOSCLEROSIS (24 E)

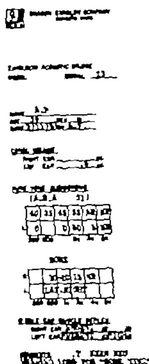
X OSSICULAR SEPARATION (4 E)

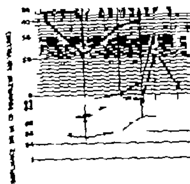
FIG 4 Median compliance (abov) and resi tance values t the ardrum f ormal, and otoscleroti rs, nd e rs with os icular separation The compliance i plotted n a loga ithmi scal th resista c n a lin a e A standard II I I form ha been sed for this and the following plots.

ance The resistance is somewhat increased in the presence of otosclerosis, and is clearly decreased by ossicular separation

Maybe I should mention that the data are plotted on standard clinical forms which also include space for results of other tests The compliance is plotted on a logarithmic scale the resistance on a linear one

Now I would like to show you some individual cases which may be of interest to you The next slide (Fig 5) shows audiometric and acoustic results on a patient who was referred as a probable unilateral otosclerotic The audiometric test shows a typical air bone gap right and a normal hearing at low frequencies left On the acoustic plots, the shaded areas indicate the ranges of 80 of ears with normal hearing The compliance of the left ear fits neatly within this range the resistance is just a little





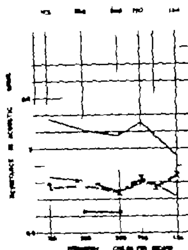
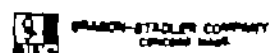


Fig. 5. Compliance and resistance measured at the eardrum of a patient with unilateral ossicula separation. Note absence of muscl refl in the affected ear. Shaded area indicat the ra ge of 80% of clinically normal ears.

bel w it. In the right ear the compliance is increased by a factor of more than two and the resistance decreased to about one-third. These results clearly indicate an ossicular separation. The operation performed subsequently uncovered an erosion of the long process of the incus.

Results obtained on a very different case are shown in the following slide (Fig. 6). The patient was referred on a medico-leg l consultati n following a claim of hearing loss in the left ear as a result of a blow to the head. The audiometric air bone gap in the left ear led to a tentative diag nosi of ossicular separation. However the acoustic examination revealed a low compliance coupled with a nearly normal resist nce—a result consistent with an otosclerotic stapes ankylosis. Surgery confirmed the latter diag nosis.

Incidentally please not the reduced compliance in the contralateral ear with practically normal hearing. This ymptom i often found in cases



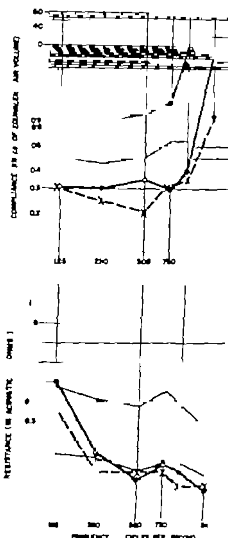


FIG. 6 Results of acoustic x mination of a pati t with asymm trical otosel rotic ankylosis.

of unilateral otosclerosis and appears to indicate an early stage of stapedial fixation

If you looked only at the audiometric results of the next slide (Fig 7) you would probably conclude that you have a case of sensori neural hearing loss before you However the acoustic compliance is drastically reduced, particularly in the left ear which has the greater hearing loss The resistance is high This pattern is consistent with massive adhesions to the incus or even malleus. Dr Shea operated and found light otosclerosis accompanied by massive adhesions

I don t have enough time for more individual cases, but I would like to show you some postoperative acoustic measurements Dr Feldman of the New York Upstate Medical Center had the opportunity to examine three small populations of patients with different types of stapedial prostheses The next slide (Fig 8) shows the median compliance and resistance values

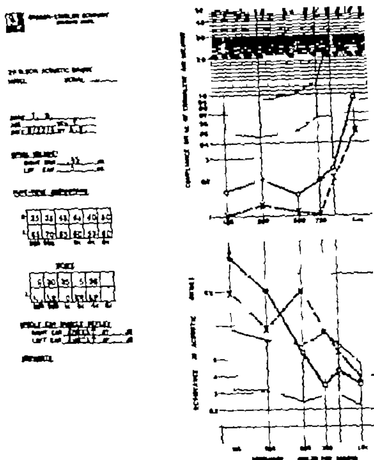
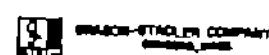


Fig. 7 Result of acoustic examination on patient with otosclerosis and nasal effusion. Note the ambiguous audiometric results.

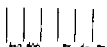
be obtained. Both the wire fat and the teflon prostheses have produced a larger than normal compliance and smaller than normal resistance. This indicates a weakened coupling with the inner ear and could possibly account for some of the residual postoperative hearing loss. The stainless steel prosthesis produced on the average approximately normal compliance and resistance values, but the resonance point seems to have been shifted toward the lower frequencies. This is consistent with an increased effective mass.

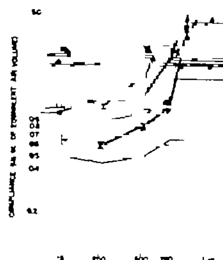
What I have shown you does not exhaust the applications of the acoustic method. *Through detection of the acoustic muscle reflex*, the method has been applied to cases of Bell's Palsy *and to the determination* of loudness recruitment. In conjunction with the Valsalva maneuver or similar procedures it also permits testing of the *Eustachian tube*.

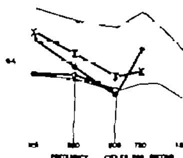
The acoustic method is now being used at several clinics in this country











ZWISLOCKI ACOUSTIC BRIDGE
MODEL SERIAL 1
NAME MEDIALS
CANAL VOLUME
RIGHT EAR cc
LEFT EAR cc
PURE TONE AUDIOGRAMS
MIDDLE-EAR MUSCLE REFLEX
RIGHT EAR AT dB
LEFT EAR AT dB
COMMENTS
PROSTHESES
O WIRE FAT (8 E)
TEFLON (1 E)
X STAINLESS STEEL (11 E)

FREQUENCY CYCLES PER SECOND

Fig. 8 Median compliance and resistance at the eardrums of patients with stapedial prostheses.

and abroad. The next 10 or 15 years will show whether it will become accepted as a routine method of ear examination. This seems to be the average time lag between research and clinical practice.

RESUME

La recherche acoustique récente qui emploie des instruments améliorés et l'analyse rigoureuse a amené une compréhension détaillée de la fonction normale et pathologique de l'oreille moyenne et une nouvelle méthodologie diagnostique. Cette méthodologie est complémentaire de l'audiométrie. Cette dernière est enrichie par l'application de quelques résultats de la recherche psychoacoustique sur les phénomènes de la sommation temporelle et de l'adaptation.

ZUSAMMENFASSUNG

Kürzliche akustische Untersuchungen, bei denen verbesserte Instrumente und genaue Analyse angewandt wurden, haben zu einem recht detaillierten Ver-

ständnis der normalen und pathologischen Funktion des Mittelohrs und zu einer neuen diagnostischen Methodik geführt. Diese Methodik ergänzt die Audiometrie. Die letztere wird durch die Anwendung einiger Ergebnisse der psychoakustischen Untersuchungen über da Phänomen der Zeitintegration der akustischen Energie und der Adaptation erweitert.

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DISCUSSION

F Escher What is the influence of the pneumatisati n of the mastoid n M Zw lock experiments? Especially in the case of total fixation of the os icular chain w must adm t a tympanosclerosis, in which we find generally a lacking pneumatisation.

F Altmann W has been using Mr Zwislocki' acoustic bridge in the Presbyteria Hosp tal for a while nd f d it an xtremely useful di gnost tool. I want to ask Dr Zwislock if he k ows of a method of temporarily losing, for the time of examination, perforation in the drum m mbran so that the coustic bridge could also be used in these cases before performing a tympanoplasty

G Lidén In your presentation you mentioned that t 1000 Hz the middle ear is inf n t l compliant From thi po nt of view how d you feel bout th choice f 800 Hz as a carrier frequency in the coustl bridge developed by Møller d would you care t om ment on th

J J Zwislocki (Reply) to Mr *Escher* The middle ea ca ities have little ffect on the acoustic properties of the human middl ea at l w sound fre quen ies. This is in contradistinction t conditions in th middle ea of small mammals where the acoustic properties t low frequencies are almost completely

determined by the air volume of the bulla The compliance measured at the eardrum may be reduced drastically in pathologies other than tympanosclerosis. It is quite sensitive to adhesions to the large ossicles and even viscous fluid can bring it almost to zero

to Mr *Altmann* Technics of closing eardrum perforations are not my territory and I would be very reluctant in making any suggestions. We have never attempted to measure the acoustic properties of the middle ear in the presence of tympanic perforation However the compliance and resistance of the middle ear are not sensitive to eardrum properties and any light material placed over a portion of the eardrum should permit acoustic measurements without negatively affecting their results.

to Mr *Lidén* Møller's suggestion is to measure the acoustic reflex at 800 Hz. We have been using 750 Hz for similar determinations. In some ears, the change of acoustic properties due to muscle contraction is very strong in this frequency region However in other ears it is hardly noticeable. The reflex effect appears to be more stable at 250 and 500 Hz As a consequence we usually test it at two or three frequencies

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ON COCHLEAR SHARPENING AND CROSS-CORRELATION METHODS

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Responses of single fibres in the cat's auditory nerve due to white-noise stimulation were recorded on magnetic tape The stimulus and the series of action potentials (spikes) were subsequently analyzed with the help of an average-response computer" M tters were arranged in such a way that the computer verages the noise-wa eshape fragment during a certain period prior to each spike In this way the causative phenomena behi d the excitation of the auditory neuron reveal themselves and can be further analyzed.

It is a well known fact that the cochlea is capable of a limited amount of frequency resolution. Low tones are directed at the apical end, and high tones at the basal end At a given spot along the basilar membrane a tone *of a specific frequency produces a maximal vibration amplitude Tones of* different frequencies give les amplitude at that point. For lower frequen cies the amplitude goes down with about 10 dB per octave for higher fre *quencies this is about "0 dB per octave (Fig 1) At the level of the auditory* nerve however things are different. One given fibre of this nerve can give rise t a sound provoked discharge (in the form of a more or less irregular series of *action potentials or "spikes") but this depends on the frequency* and intensity of the tone A fibre is most sensitive to a particular frequency the so-called characteristic frequency (C.F) Frequencies lower than that *need to be presented at higher intensity about 30 dB/octave* more Frequencies bove th characteristic frequency must be presented at considerably higher intensities before a response is obtained the slope amounts to 100–400 dB/octave

The cochlea and auditory nerve both ha e the property that the slope at higher frequ ncies is the steeper one But there is no further similarity between the data. The audit ry nerve i considerably *more frequency* selective than the cochlea. Between the level of cochlear movements and the excit tion f nerve pulses there mu t be a sharpening mechanism That mechani m makes the frequency response sharpe *providing a sharper cut* off f r frequencies deviating from the characteri tic frequency (Fig 2)

It is a remarkable property that the slope at the high-frequency nd of each tuning curve is very high, 100–400 dB/octave (by technical standards tremendously high) Technical filt rs have a cut-off slope of the order of

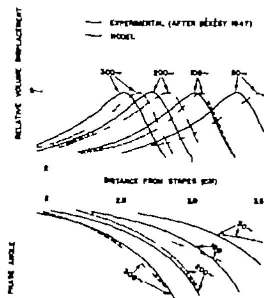


Fig 1



Fig 2.

Fig. 1 Frequency resoluti n in the cochlea frequency respo se at va ious points along sid the ba llar membrane From W M Si bert (1962)

Fig 2. "Tuning curve of auditory neuro s. The graph shows the frequencies (horizontal scal) and intensities (vertical scale) of all t nes th t give a threshold respo se A ton outside th tuning curve gives no response From Th. Wei s (1964)

6 12, 18 or 24 dB/octave It is rather difficult to make a filter that cuts off at a much faster rate

On the problem of this cochlear sharpening mechanism a few theories are proposed One is that the auditory nerve fibres, in their course along several hair cells of the organ of Corti act as gates They are supposed to pass a pulse only when a number of hair cells gives off an impulse in just the right time order One may say that this process resembles the action of a synapse in the CNS, although no synapse is actually involved A critical factor in this theory is a.o the speed of propagation of a pulse along the auditory nerve fibre from one hair cell to the other

A second theory assumes that the stimulation of any hair cell is already a complicated affair It is not simply the movement of the basilar mem brane that stimulates a hair cell but a more complicated function A hair cell is supposed to be subjected to a combination of forces, compressional and shearing It is thought that a proper combination of influences can be the source of *cochlear sharpening*

At present there is no reason to prefer one theory over the other The point is that there have been no reports on the signals that propagate along the nerve fibres in their course from hair cell to hair cell There is even insufficient knowledge on the number of hair cells that are connected to a given fibre

In our laboratory this problem has been studied in a completely new

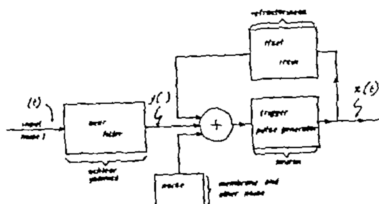


Fig. 3. Simplified model of dilory nerve excit tion, after Th Weiss (1964)

way The method is a mathematical procedure that does not require access to an intermediate stage and yet gives information about the cochlear transformations (de Boer & Kuyper) Fig 3 gives a simplified model of how we could assume an auditory neuron to be excited. The incoming acoustic signal is modified by cochlear filtering a given location is maxi mally sensitive to a specific frequency

Whenever the output signal surpasses a certain threshold, a nerve im pulse is generated. To allow for spontaneous nerve spikes in the absence of acoustic input an independent noise source must be introduced. The actual model is still more complicated but for our purpose this is sufficient. The problem is now that we should like to know more about the inter mediate signal y (t) but we cannot reach this stage experimentally Cor relation theory now provides an answer If one would stimulate the entire system with white noise, and if one could study the signal y (t) then one could compute the cross-correlation function of x (t) and y (t) In com puting a cross-correlation function, a value x (t) is multiplied with the value y $(t+$ $)$ taken seconds later This is done for many values of t but with fixed and the resulting product is averaged over all time The answer is a function of that represents the average resemblance between values of x and y taken seconds apart in time

If we now instead of x (t) and y (t) process x (t) and z (t)—this being the train of nerve spikes—the *result* would be very much like the true cross-correlation function That means that it is experimentally possible to deri e the cross-correlation *function (CCF)* over the cochlear filter" by processing on input and output signals of the entire system. There is an important theorem that says for white n ise stimulation the input-output CCF of a filter is equal to the filter's "impulse response" This is th output f the filter when the input i a very sharp impulsive signal This all means that we re able, just by utilizing input and output of th cochlea, to find out all about the system labelled linear filter in the model

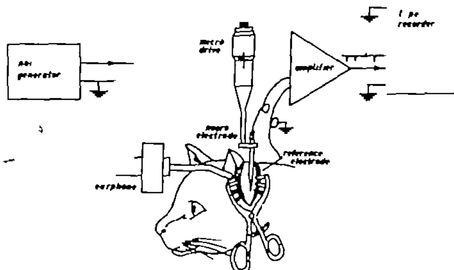


FIG 4 Block diagram of the experimental set up.

The next figure (Fig 4) shows the experimental set up The cat s skull is opened, a portion of the cerebellum is sucked away and a glass micro-electrode is inserted until contact is made with a neural unit in this case a primary auditory nerve fibre

The animal s ear is stimulated with white noise, presented via an ear phone Both the white-noise stimulus and the ensuing train of nerve pulses are recorded on magnetic tape Computation of a cross-correlation function generally is a quite complicated process. In this case it is much simpler a computation run is done for each nerve spike when no spike is present nothing need to be done The computation is performed with help of an *average response computer* Such a computer is able to determine the aver age waveform of an incoming signal It must be set into action—synchronized—by a pulse

When it receives a pulse it adds the incoming signal s waveform during a specified period to the waveform already present in the computer s memory In the normal way of operation this instrument is capable of retrieving any average waveshape that is time-locked to the occurrence of synchronization pulses This is possible even when the response is drowned in noise In our case the computer is utilized in the *reverse* way It is synchronized, not by the stimulus, but instead by the output of the prepara tion The output the series of action potentials, is converted into a series of neat pulses and these pulses synchronize the computer After receipt of a pulse the computer is ready to process a signal This signal is shown in Fig 5

On replay of the tape recorder we have two signals, the action spikes of the neuron and the input noise that caused them As stated before the action spikes synchronize the computer The input noise is fed to a second

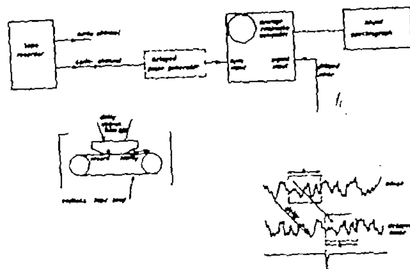


Fig. 5. Signal processing. The action spikes synchronize the computer. The white noise which originally causes them is delayed in time. The computer next determines the average waveshape of the delayed noise over a certain period after the spikes (see text).

tape recorder one that is provided with an endless loop of magnetic tape. Shortly after this white noise is recorded it is replayed, being picked up by a replay head on the recorder. In that way we have exactly the same signal gain, but delayed in time.

What occurred earlier now appears at a later moment. Now suppose the computer is set into action by the receipt of a nerve spike and we give it the delayed version of the noise to act on. During a specified period after the action spike the computer adds this signal fragment to the waveshape in it memory. After a few thousand nerve spikes have occurred the computer has determined the average waveshape of the delayed noise. Or in other words, after all these nerve spikes have been processed, we have the average waveshape of the noise *just prior to a nerve spike*. It gives a picture of those portions of the stimulus that have—on the average—given rise to the action spikes. The function so computed, actually is the CCF of the input-noise and the output spike signal. This function is a good representation of the cross-correlation function taken across the cochlear filter. (For the discussion of this point see de Boer & Kuyper.)

A representative example of the result of a computation is given in Fig. 6. It shows the average waveform prior to a nerve pulse. The moment the nerve pulse occurs is at the left end.

It shows an oscillatory waveform that damps out quite slowly. So this is about the shape of the CCF taken over the cochlear filter in our model. This, then, should also be the *impulse response* of the cochlear filter since white noise was given at the input.

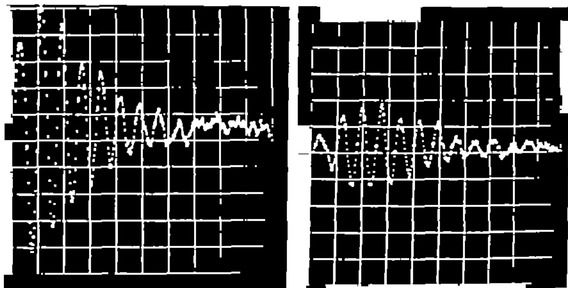


Fig 6 Typic l re ult of a comp tati n of the aver g wavef rm p l to a n rve p lse CF of unit 1 7 kHz. An lysi tim 7.5 ms. About 4000 spikes h v been processed The l ft band curve is taken t a 60 dB higher l vel than th right h nd one for the sam unit

We are now in a position to come back to the problem of cochlear sharpening If our "cochlear filter" would be the same as the mechanism of cochlear dynamics we should know what the impulse response would be

In Fig 7 the impulse response that is valid for the movement of one particular spot on the basilar membrane is shown It corresponds to the known type of cochlear filtering

The experimental results, shown in the previous figure are entirely dif ferent They show much less damping and hence must correspond to a much sharper frequency filtering As a matter of fact further study has *shown that the impulse response found corresponds to really very sharp* filtering The equivalent slope at the high frequency side ranges from 80 to 150 dB/octave for units with a CF of 500 Hz to 2 kHz. This is much higher than the slope for the cochlear frequency response It comes close to the values found for the slopes of tuning curves The value of 400 dB/ octave pertains to units with very high characteristic frequency too high to allow this type of processing Units of lower CF have somewhat lower slopes Actual values have not been measured but the similarity is satis factory so far

What conclusions can we draw from this investigation The first is that the model as it stands, is a good model for the excitation of an auditory nerve fibre Types of processing, other than those here described failed to yield anything that contradicts our model But the cochlear filter in the model does *not at all* correspond to the type of filtering that the cochlea is known to exhibit It should be more sharply tuned though still behaving like a linear network Or better like a quasi linear network i e., the frequency-dependent part behaves like a linear filter (there may be some non

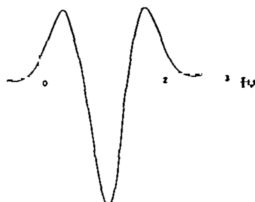


FIG. 7 Impulse response for one particula pot of the ba il membrane From W M. Siebert (1962) Not the normalized time sc le.

linearities involved but these do not affect frequency resolution) The next and ultimate question is how does this sharp filtering come about

We ha e come much closer to answering this question. It is not possible that a neuron-like interaction in the cochlea causes the sharp frequency resolution found. Such a mechanism would be completely upset by giving it white noise as a stimulus. The interaction between hair cells must be of a more subtle nature Tw possibilities can be considered

The first i that hair cell recei e a complicated mechanical stimulation, which is so ordered that the right kind of frequency selectivity arises The second possibility not yet mentioned, resides in a different kind of interac tion between hair cells. There ha been doubt about the possibility whether the first part f a fibre an actually tran mit pulses or not One may suppose that it cannot d so it can only transmit generator potentials by lectrotonic spread. Only at the pot where the fibre acquires a myelin sheath can nerve impulse originate At that spot the influences of elec trotonically propagated generator potentials add and when the sum sur pa ses the threshold, a nerve spike occurs At the moment it is not possible t stat which of these two possibilities is the most likely one There are rgument in f our of both.

CONCLUSION

The method used nd described, essentially a correlation method, is an example of one f the modern systematic approaches to the analysis of compound systems. It is clea that, since in communication engineering many similar problem arise we must keep a sharp eye on these developments. It may well be that in a completely unrelated field a problem is

solved by a method that is applicable to our problem A team of specialists, not just one man trying to be universal is needed

Such a team should include apart from the otologist, a physicist (or communications engineer) and, in our case a neurophysiologist. We were fortunate in having at our disposal all the required facilities in this respect as well as the people

RÉSUMÉ

Les réponses évoquées par bruit blanc dans les fibres du nerf auditif du chat ont été enregistrées sur bande magnétique Le stimulus et les séries de potentiels d action ont ensuite été analysées à l aide d un average-response computer On s est *arrangé d une telle façon que le computer fait la moyenne des fragments* d ondes du bruit qui précèdent chaque potentiel d action pendant une certaine période Ainsi les causes de l excitation du neuron auditif se révèlent et peuvent être analysées

ZUSAMMENFASSUNG

In Einzelfasern des Nervus acusticus bei der Katze wurden die von einem weissen Geräusch verursachten elektronischen Effekte auf Magnetophonband registriert Der Reiz und die Reihe von Aktionspotentialen (Spikes) wurden dann analysiert mit Hilfe eines „average response computer" Die Aufstellung war derartig dass der Computer einen Mittelwert der Wellenform während einer gewissen Zeitspanne vor jedem Spike bildete Die ursächlichen Phänomene der Reizung des akustischen Neurons zeigen sich in dieser Weise und können weiter analysiert werden

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DISCUSSION

H Davis The problem attacked by Mr De Boer and Mr Jongkee i probably the most basic unsol ed problem of cochlear physiology The experiments reported give important additional information and we hope for a firm nterpretation shortly What is the range of frequencies for which such correl t ons with the stimulus have been established

L B W Jongkees (Reply) The frequency one finds depend upon the neuron which is hit. They can be of v y lifferent characteristic frequencies The method works for a CF up to over 2 kHz

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ÉLECTRO-COCHLÉOGRAMME HUMAIN EN DEHORS DE TOUTE INTERVENTION CHIRURGICALE

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Bordeaux, France

Les auteurs présentent des enregistrements des potentiels cochléaires (M. C. et P A.) chez des suj t en dehors de toute i terventi n chirur gicale Ils placent l électrode au voi inage d la fenêtre ronde soit à travers une perforation du tympan lorsque celle-ci existe soit après paracentèse Utilisant un stimulation par clic, ils observent les réponses soit direct ment, soit après analyse de quelques dizaines de timulations identiques et répét tives. Si les résultats obtenus chez les sujets présen tant une perforation du tympan sont satisfaisants, il leur paraît difficile de placer *l'électrode sur la fenêtre ronde dans* les cas ou le tympan est intact. Ils pensent cependant que en piquant un électrod sur le pro- montoire à tra ers le tympan il sera possibl de mettre au point un électro-cochléogramme pou lequel l'utilisation et d'un stimulation répét tive par clic et d un moyen eur est i dispensable

Depuis la découverte par Wever et Bray en 1930 de l Effet Micro- phonique *chez le chat les réponses électriques de la cochlée à* une stimu lation sonore ont abondamment été utilisées comme moyen de contrôle de l'activité cochléaire dans une grande variété d expérimentations *sur l' nimal*, depuis les recherches fondamentales sur le processus neuro-exci tateur jusqu au contr l des manœuvres de micro-chirurgie, en passant par l étude des différents agents oto-destructeurs.

Les deux principales réponses électriques observées dan la cochlée sont

l microphonique cochléaire (M C.) signal dont la forme est, dans certaines limites, identique à celle du son in ident,

le potentiel d'action nerveux (P A) réponse à une stimulation par clic qui représente la somme des réponses cohérentes de t ut u partie des f bres nerveuses à l'intérieur de la cochlée

Parallèlement à ces mesures chez l animal, quelques essais ont été faits pour mesurer ces potentiels *che l'homme* Depui 10 ans environ, grâce au progrès technol gique des résu t ts de plus en plus intéressants sont ob- ten s, et ces mesures sont passées du stade de la recherche pure à celui des application cliniques a ce en particulier les observations de Ruben *et al* et d ll n d n différent ca de urdité (Ronis, 1966 Ruben *et al* 1967 Ruben & W lker 1963 Ruben, 1965

Nou a ons pens qu de telles mesures seraient peut-être applicables à l' udiométrie En effet le microchirurgien otologist se trouve parfois de nt des cas, certes rares, où il est délicat d décider d une intervention chirurgicale ur l'oreille moyenne l audiogramme st difficile à interpré-

Attaché de Recherche à l I.N.S.E.R.M

ter et l on ne peut certifier que la surdité est d origine interne ou de trans mission Dans ces cas là il est évident que si l on pouvait disposer d une indication précise sur le fonctionnement réel de la cochlée, la décision d intervenir ou non sur l oreille moyenne serait grandement facilitée.

Cependant l enregistrement des réponses électriques de la cochlée chez l homme présente deux difficultés majeures

— d une part les réponses enregistrées au niveau de la fenêtre ronde sont très faibles et souvent masquées par le bruit de fond

— d autre part les enregistrements réalisés par la plupart des chercheurs ont été faits au cours justement d interventions chirurgicales sur l oreille

Il va de soi que si on veut utiliser ces mesures pour l audiométrie, il faut les réaliser en dehors de toute opération et sans trop de désagrément pour le patient

C est ce que cette année, nous avons essayé de réaliser dans notre Laboratoire mettre au point une technique permettant d enregistrer les potentiels cochléaires en dehors de toute intervention chirurgicale et voir si l on peut attendre, des réponses ainsi enregistrées, une indication valable sur le fonctionnement de la cochlée

METHODES

1 *Mode opératoire*

Nous avons systématiquement essayé d enregistrer les réponses cochléaires chez des sujets qui présentaient une perforation du tympan de telle sorte que la fenêtre ronde soit visible, puis, lorsque la méthode d enregistrement des réponses a été au point, nous avons essayé, chez des sujets présentant un tympan intact d introduire l électrode à travers une microperforation réalisée après anesthésie locale

— Le sujet est allongé sur une table d examen dans une pièce insonorisée et faradisée

— Un spéculum d oreille est maintenu dans le conduit auditif externe au moyen d une bande adhésive de telle sorte qu il n est solidaire que de la tête du sujet lui laissant ainsi une certaine liberté de mouvement

— L électrode de masse est soudée au spéculum

— Sous microscope opératoire, l électrode active est placée dans la niche de la fenêtre ronde C'est un fil de Nickel-Chrome de 50 microns de diamètre dont l extrémité est dénudée et applatie

— L électrode indifférente de même nature est posée sur le promontoire ou piquée dans le conduit auditif externe

2° *Stimulation*

Nous n avons utilisé que la stimulation par clic, pour plusieurs raisons

— Le clic évoque à la fois une réponse microphonique et une réponse nerveuse qui sont facilement mesurables.

— En outre il est moins traumatisant pour l oreille de stimuler aux fortes intensités, par un son tr s bref que par un son pur permanent

— De plus l'enregistrement des réponses à des sons purs de différentes fréquences et intensités aurait prolongé considérablement l'examen, mettant par trop à l'épreuve la patience du sujet.

— Enfin les réponses microphoniques à des sons purs sont faibles, et il est souvent difficile d'y discerner les réponses réelles des artefacts, en particulier du passage par influence du signal électrique de stimulation.

Certes une stimulation par clic ne peut donner d'indication sur la sensibilité en fréquence de la cochlée, mais, étant donné que les atteintes de l'oreille interne affectent principalement les aigus, c'est à dire se situent au premier tour de spire nous pensons que la présence de potentiel d'action aux faibles intensités et de microphonique et potentiel d'action aux fortes intensités sont des indications suffisantes sur le fonctionnement du premier tour voire de toute la cochlée.

— Le clic est donc produit (Fig. 1) par des impulsions rectangulaires de 0,1 ms de largeur qui, à travers des atténuateurs et un amplificateur Basse Fréquence, attaquent un moteur de haut parleur convenablement blindé. Le son est conduit alors à l'oreille du sujet à travers un tube souple terminé par un petit pavillon dont le diamètre est légèrement supérieur à la dimension de l'oreille externe. Celui-ci est, au cours de la stimulation, placé à un demi-centimètre de l'oreille. Cet espace est propre à atténuer considérablement la transmission du ronflement résiduel.

Cet équipement a été calibré en décibels par rapport *au seuil moyen d'audition du clic* chez un certain nombre de sujets normaux. On peut ainsi obtenir des clics jusqu'à 140 db au-dessus du seuil.

3° *Enregistrement des réponses*

Les trois électrodes, active, indifférente et masse sont reliées à un pré-amplificateur Tektronix de gain 1000 qui attaque d'une part une voie d'un oscilloscope C.R.C. double trace, d'autre part, à travers un amplificateur supplémentaire, une voie d'un enregistreur magnétique Ampex SP 300 (Fig. 1). La bande passant du pré-amplificateur est fixée

de 80 à 1000 Hz, quand on veut observer les réponses directement sur l'oscilloscope

de 8 à 10 000 Hz quand on veut les enregistrer sur l'Ampex.

Le synchronisation issue du générateur d'impulsions est envoyée sur l'oscilloscope et sur une autre voie de l'enregistreur magnétique. Enfin les commentaires sont enregistrés sur une troisième voie. Etant donné la faible Band Passant de l'enregistreur en modulation de fréquence nous avons préféré utiliser l'enregistrement direct. Le signal enregistré sur l'Ampex est simultanément lu et envoyé sur la deuxième trace de l'oscilloscope de façon à surveiller la qualité de l'enregistrement.

4° *Mesure*

Les réponses visibles sur l'oscilloscope pour différentes intensités sont aussitôt photographiées sur film Polaroid. On détermine assez difficile-

ter et l'on ne peut certifier que la surdité est d'origine interne ou de transmission. Dans ces cas là, il est évident que si l'on pouvait disposer d'une indication précise sur le fonctionnement réel de la cochlée, la décision d'intervenir ou non sur l'oreille moyenne serait grandement facilitée.

Cependant l'enregistrement des réponses électriques de la cochlée chez l'homme présente deux difficultés majeures:

— d'une part les réponses enregistrées au niveau de la fenêtre ronde sont très faibles et souvent masquées par le bruit de fond;

— d'autre part les enregistrements réalisés par la plupart des chercheurs ont été faits au cours justement d'interventions chirurgicales sur l'oreille.

Il va de soi que si on veut utiliser ces mesures pour l'audiométrie, il faut les réaliser en dehors de toute opération et sans trop de désagrément pour le patient.

C'est ce que, cette année, nous avons essayé de réaliser dans notre Laboratoire: mettre au point une technique permettant d'enregistrer les potentiels cochléaires en dehors de toute intervention chirurgicale et voir si l'on peut attendre des réponses ainsi enregistrées, une indication valable sur le fonctionnement de la cochlée.

MÉTHODES

1. *Mode opératoire*

Nous avons systématiquement essayé d'enregistrer les réponses cochléaires chez des sujets qui présentaient une perforation du tympan de telle sorte que la fenêtre ronde soit visible, puis, lorsque la méthode d'enregistrement des réponses a été au point, nous avons essayé, chez des sujets présentant un tympan intact, d'introduire l'électrode à travers une microperforation réalisée après anesthésie locale.

— Le sujet est allongé sur une table d'examen dans une pièce insonorisée et faradisée.

— Un spéculum d'oreille est maintenu dans le conduit auditif externe au moyen d'une bande adhésive de telle sorte qu'il n'est solidaire que de la tête du sujet, lui laissant ainsi une certaine liberté de mouvement.

— L'électrode de masse est soudée au spéculum.

— Sous microscope opératoire, l'électrode active est placée dans la niche de la fenêtre ronde. C'est un fil de Nickel-Chrome de 30 microns de diamètre, dont l'extrémité est dénudée et applatie.

— L'électrode indifférente, de même nature, est posée sur le promontoire ou piquée dans le conduit auditif externe.

2° *Stimulation*

Nous n'avons utilisé que la stimulation par clic pour plusieurs raisons:

— Le clic évoque à la fois une réponse microphonique et une réponse nerveuse qui sont facilement mesurables.

— En outre il est moins traumatisant pour l'oreille de stimuler, aux fortes intensités, par un son très bref que par un son pur permanent.

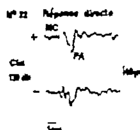


Fig. 2.

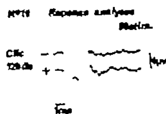


Fig. 3.

Fig. 2 et 3. Mise en évidence du changement de phase du microphonique cochléaire par rapport au potentiel d'action lors de l'inversion de la stimulation.

tion simultanée au clic d'un bruit blanc. Ce phénomène est très net, que le bruit blanc soit produit par un générateur électronique ou par un chuintement labial à l'oreille du sujet. Cet effet n'a pas encore été contrôlé sur l'Analyseur et une étude plus détaillée devra être entreprise.

Voici quelques exemples des réponses ainsi enregistrées chez certains sujets

Sujet nº 22 (Fig. 5) l'oreille gauche présente une perforation que reflète bien l'écart des courbes de conduction osseuse (C. O.) et conduction aérienne (C. A.) la conduction osseuse étant relativement bonne. A partir de 110 db on obtient une très bonne réponse au clic, visible directement sur l'Oscilloscope. Grâce à l'Analyseur on voit qu'entre 80 et 90 db on a encore une réponse

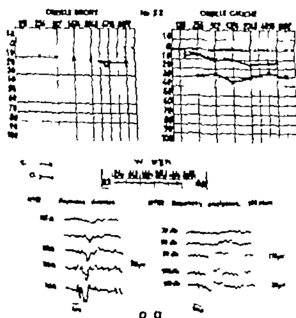


Fig. 5. Sujet 22 audiogramme et réponses enregistrées pour l'oreille gauche

ment certes, le seuil des réponses visibles sur l'oscilloscope En partant alors de 40 db en-dessous de ce seuil, on réalise des séries de stimulations identiques à raison de 6 clics par seconde, les signaux correspondant étant enregistrées sur l'Ampex. L'on procède ainsi pour des intensités croissantes de 10 en 10 db jusqu'à l'intensité pour laquelle on a une réponse directe nettement visible à l'oscilloscope Lorsque pour certains sujets, aucune réponse n'était bien visible directement on réalisait néanmoins l'enregistrement à des stimulations répétitives de 100 à 130 db

Grâce à l'obligeance de l'entreprise « l'Electronique appliquée » qui réalise entre autre du matériel médical nous avons pu utiliser l'Analyseur Multicanaux « Elatron 1000 » pour analyser les réponses ainsi enregistrées chez une douzaine de sujets Utilisant sa fonction moyenneur les signaux répétitifs sont additionnés de telle sorte que l'on peut extraire la réponse moyenne du bruit de fond dans laquelle elle était noyée

RÉSULTATS

En réponse au clic nous obtenons donc le microphonique cochléaire immédiatement suivi du potentiel d'action Nous avons pu vérifier les caractéristiques classiques de ces réponses qui garantissent leur nature physiologique, que ce soit sur une réponse directe ou sur la sommation de nombreuses réponses dans l'Analyseur

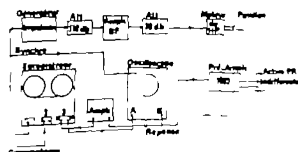
Ce sont

— l'inversion de la phase du microphonique cochléaire le potentiel d'action gardant le même sens négatif quand on inverse la polarité de la stimulation (Figs 2 et 3) (les réponses sont enregistrées de telle sorte que les pics négatifs sont dirigés vers le bas)

— la latence du potentiel d'action par rapport au microphonique entre 1 et 2 ms (Figs 2 et 4)

— l'augmentation de cette latence avec la diminution de l'intensité du clic (Fig 5 et suivantes)

— l'effet de masque produit sur le potentiel d'action par la présenta



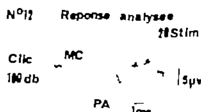


Fig 1 Fig 4

Fig. 1 Schéma de l'appareillage

Fig. 4 Exemple de réponse analysée sujet n° 12

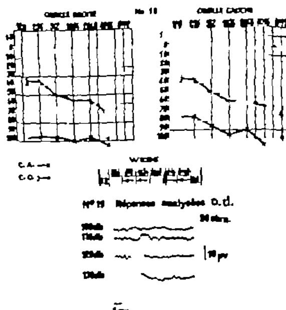


Fig. 7 Sujet n° 10 diegramme et réponses analysées pou l'oreill droite.

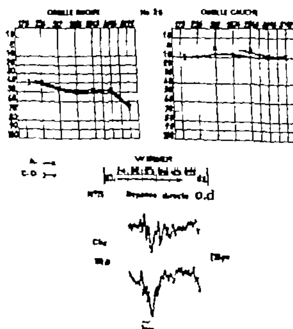


Fig. 8 Sujet n° 25 udiogramme — réponses clic à 100 db (+ et –) l'électrode) ait été introd après paracentèse

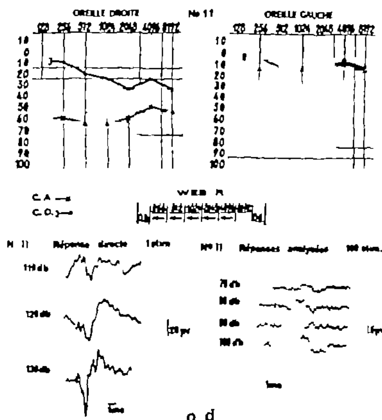


FIG 6 Suj t n 11 — udiogramme et réponse enregistrées pour l oreille droite

L ensemble des traces montre bien en outre la variation de la latence du potentiel d action avec l intensité de la stimulation

Sujet n 11 (Fig 6) l oreille droite présente une perforation à laquelle s ajoute une surdité de transmission et une chûte en voie osseuse pour les aigus Cependant on obtient encore de bonnes réponses et sur l Analyseur on distingue encore une très légère réponse à 70 db

Sujet n 19 (Figs 4 et 7) forte surdité bilatérale à la fois de transmis sion et de perception

Pour l oreille droite qui présentait aussi une perforation il était difficile de déceler une réponse directement sur l Oscilloscope mais, à travers l Analyseur les réponses sont nettes à 120 et 130 db, puis beaucoup plus faibles déjà à 110 db

Sujet n° 26 (Fig 8) surdité de perception chûte de 40 à 50 db pour l oreille droite qui ne présentait pas de perforation aussi l électrode a t-elle été introduite, au voisinage de la fenêtre ronde à travers une micro-per foration réalisée dans le tympan Malgré beaucoup de bruit de fond une bonne réponse directe est observée à 100 db, l inversion du clic laissant in changée la phase de la réponse nerveuse

Sur les 27 sujets que nous avons testés

— les premiers ont uniquement servi à mettre au point les méthodes de stimulation et d enregistrement

ZUSAMMENFASSUNG

Di Aut ren untersuchen seit mehreren Jahren menschliche Elektrocochleogramme w lche ohne irgendeine operative Behandlung registriert werden. Die 1967 i Bordeaux veröffentlichte M thode gestattet die Aufnahme eines Elektrocochleogramm bei kranken entweder mit perforiertem oder mit normalem Trommelf ll. Die Ergebnisse werden in V rbindung mit beso deren klinischen F llen analysiert deren Knochenleitu g mit der üblichen Methode der Audiometrie nicht in einwandfreier W ise untersucht werden konnt Obgleich sie ungergewöh lich ist, unterstreichen die Autoren die Bedeutung ein r solchen Method f r das Anzeigen gewisser chirurgischer Eingriff

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Faculté de Médecine Bordeaux F ance

— Nous avons obtenu des réponses, plus ou moins importantes suivant l audition du sujet et la qualité du positionnement de l électrode, chez 16 sujets dont tous, sauf 2 présentaient une perforation

— Parmi les sujets pour lesquels nous n avons pu obtenir de réponses 4 étaient pratiquement sourds totaux pour 4 des 6 sujets chez lesquels l électrode était introduite après paracentèse du tympan, l électrode n a pu être mise en place correctement malgré plusieurs essais et les enregistrements *étaient saturés de bruit enfin chez les autres sujets, un manque de* coopération de leur part rendait impossible toute mesure

CONCLUSION

L enregistrement des réponses cochléaires chez les sujets présentant une perforation du tympan est relativement aisé en plaçant l électrode dans la niche de la fenêtre ronde, et les moyens dont nous disposons actuellement permettent de les mesurer correctement

Par contre, il semble difficile de placer l électrode sur la fenêtre ronde à travers une micro-perforation du tympan avec suffisamment de chance de succès. Lempert *et al* (1950) avaient, dès 1950 fait cette constatation lors qu ils essayaient d enregistrer par cette méthode, le microphonique cochléaire

Cependant il ne faut pas pour autant abandonner l'idée de réaliser un test audiométrique par l observation des potentiels cochléaires. En effet, après nos propres recherches et les travaux de Yoshie *et al* (1967) (qui enregistrent la réponse nerveuse en plaçant une électrode dans le conduit auditif externe et additionnent un grand nombre de réponses dans un moyenneur) nous sommes certains que

— l utilisation de la stimulation par clic

— la mise en place d une électrode sur la fenêtre ronde quand cela est possible, ou bien systématiquement piquée sur le promontoire à travers une micro-perforation du tympan

— et surtout l utilisation d un Analyseur Moyenneur vont permettre la mise au point définitive d un test Electrocochléogramme » dont l utilisation limitée à certains cas particuliers, sera d un grand intérêt pour l audiométrie

SUMMARY

Within the last few years the authors have studied the human electrocochleogram recorded without a surgical procedure This method published in 1967 in Bordeaux allows the recording of an electro-cochleogram on patients with either a tympanic perforation or a normal drum These results are concerned with particular clinical cases on which the bone-conduction curve had never been accurately tested by routine audiometry Though exceptional the authors mention the interest of such a method especially as a help for indication for certain surgical operations.

Acta oto-laryngologica 45, 111-119 (1948)

HISTOLOGICAL FINDINGS IN CONGENITAL DEAFNESS

F. ALTMANN, M.D.

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Histological findings in congenital deafness fall into two groups. The first group is haracterized by changes resembli g those observed in healed mild serous or viral labyrinthiti (maternal rubella) o in mild "posthydropic neuroepithelial dege eration The ther group presents purely degenerative atrophic hanges resembling to certain degree those of mild genui neuroepithelial degeneration The hypothesi is considered that the changes found in both groups could be the result of certain types of m lfuncti n of the stria scolari whi h interfere with the ability of the stria to maintain the n rmal chemical constitution of the end lymph This possible explanation is put forth in view of the similarities between the changes produced by genetic and the changes produced by extri sic fa tors.

The anat mical findings in what is commonly called congenital deafness (i.e. deafness present at birth) can be divided into two groups one group with regressive changes in the epithelial structures of the cochlear duct, the saccule and occasionally the utricle, their nerves, ganglia and central pathways, and another group with evident anatomical anomalies of the cochlea and sometimes also of the other parts of the inner ear

The regressive changes characterizing the first group develop either "spontaneously" without any apparent extrinsic cause, or secondary to known extrinsic factors, such as virus diseases. "Spontaneous" regressive changes and outright developmental an malies form the basis of genetically determined (inherited) deafness, "secondary" changes the basis of acquired deafnes

The m j rity of the malf rmations of the inner ear in genetically determined deafness are f und without changes in other parts of the ear Some of the inner ear malform tion occur with the group of combined malformation of the external and middle ear known a atresia auris congenita Stil thers are observed in non-viable fetuses, associated with devel pmental anom lies f the central nervous system al ne or combined with malformations f the external nd middle ear

Our knowledge f the spontaneou regressive changes is still limited. On group of cases, the so-called cochleo-saccular or *Scheibe* type is charcterized by epith li l changes in the cochlear duct and its contained structures, the saccule sometimes also their nerves, ganglia and their central

Thi work pported by grant NB 6-3376 (61A of the National Institut of Health nd by the Research F nd of the America Otological Societ

DISCUSSION

H. Davis: It is interesting to see how similar studies are made simultaneously on opposite sides of the world and how well the results agree. My former colleague Mr. Yoshie, now at Matsumoto in Japan, has reported very similar experiments in the *Laryngoscope*. Mr. Yoshie's technique differs in that he places the active electrode in the wall of the external auditory canal. He obtains good action potential responses to clicks, but in a recent letter he writes to me that he has had much greater difficulty when he uses filtered clicks or tone bursts as stimuli.

J. E. Bordley: I would like to express my appreciation and enjoyment of Mr. Portmann's excellent presentation. The work on human cochlear responses to sound stimuli should be continued in order to give us as much information as possible on the activity of the functioning human peripheral endorgan in life.

Two remarks occurred to me while listening to Mr. Portmann's essay. First, the delay time between stimulus and the appearance of the nerve action potential as the intensity of the stimulus was increased appears to be shortened. This change in delay would seem reasonable but we have not recognized this in our results. We will be interested in looking for such changes in our future recordings.

After seeing the charts presented today, the question arises if the essayist has noted a closer relation between the threshold of hearing and the appearance of the nerve action potential in severely hard of hearing patients than in the mildly deafened patient.

The use of computers in studies of cochlear potentials and nerve action potentials has proven much simpler in the latter. Much, I am sure, could be learned if we can develop better application of the computer to cochlear responses to pure tones.

Mr. *Portmann* (Réponse): à Mr. *Davis*: Je peux répondre qu'effectivement Y. Yoshie au Japon a publié un travail dans le *Laryngoscope* en même temps que nous dans la *Revue de Laryngologie*. Il sera intéressant de suivre les progrès de leurs méthodes.

à Mr. *Bordley*: Je peux dire que son commentaire était, pour moi, important puisque son Service traite ces problèmes depuis 10 ans très activement. Nous n'avons pas trouvé de relation entre le niveau du potentiel d'action et le seuil subjectif. Cette relation ne nous a pas paru plus précise quand le malade était plus sourd, mais d'autres "data" sont encore nécessaires.

Acta oto-laryngologica 65, 114–119 (1968)

HISTOLOGICAL FINDINGS IN CONGENITAL DEAFNESS

F. ALTMANN, M.D.

From the Department of Otolaryngology, College of P. & S., Columbia University and the Presbyterian Hospital, New York City, N.Y., U.S.A.

Histological findings in congenital deafness fall into two groups. The first group is characterized by changes resembling those observed in healed mild serous or viral labyrinthitis (maternal rubella) or in a mild "posthydropic" neuroepithelial degeneration. The other group presents purely degenerative atrophic changes resembling to a certain degree those of a mild genuine neuroepithelial degeneration. The hypothesis is considered that the changes found in both groups could be the result of certain types of malfunction of the stria vascularis which interfere with the ability of the stria to maintain the normal chemical constitution of the endolymph. This possible explanation is put forth in view of the similarities between the changes produced by genetic and the changes produced by extrinsic factors.

The anatomical findings in what is commonly called congenital deafness (i.e. deafness present at birth) can be divided into two groups: one group with regressive changes in the epithelial structures of the cochlear duct, the saccule and occasionally the utricle, their nerves, ganglia and central pathways, and another group with evident anatomical anomalies of the cochlea and sometimes also of the other parts of the inner ear.

The regressive changes characterizing the first group develop either "spontaneously", without any apparent extrinsic cause, or secondary to known extrinsic factors, such as virus diseases. "Spontaneous" regressive changes and outright developmental anomalies form the basis of genetically determined (inherited) deafness, "secondary" changes the basis of acquired deafness.

The majority of the malformations of the inner ear in genetically determined deafness are found without changes in other parts of the ear. Some of the inner ear malformations occur with the group of combined malformations of the external and middle ear known as atresia auris congenita. Still others are observed in non-viable fetuses, associated with developmental anomalies of the central nervous system alone or combined with malformations of the external and middle ear.

Our knowledge of the "spontaneous" regressive changes is still limited. One group of cases, the so-called cochleo-saccular or Scheibe type, is characterized by epithelial changes in the cochlear duct and its contained structures, the saccule, sometimes also their nerves, ganglia and their central

This work was supported by grant NB 0-3370 061A of the National Institutes of Health and by the Research Fund of the American Otological Society.

pathways. In another group of cases, in the so-called *Siebenmann Bing* type, epithelial changes are noted not only in the cochlear but also in the vestibular portion of the membranous labyrinth.

The histological findings in the Scheibe type are not uniform

In some observations the changes in the organ of Corti the stria vascularis and the macula sacculi are of a purely degenerative atrophic nature with collapse of Reissner s membrane and of the saccule They resemble, to a certain extent, those experimentally produced by Wittmaack by diffusion of a solution of acetic acid through the round window membrane into the inner ear and called by him "genuine neuroepithelial degeneration"

More frequently the degenerative changes in the organ of Corti and in the macula sacculi are associated with changes in the shape and position of the tectorial membrane which is either reflected backward over the crista spiralis or tucked into the internal spiral sulcus and is covered with a single layer of flat epithelial cells The stria vascularis is atrophic but shows occasionally circumscribed papillary or fingerlike excrescences and contains, in rare instances, cysts Reissner s membrane is frequently collapsed and adherent to the stria, rarely only bulging outward Occasionally the lumen of the cochlear duct is traversed by thin strands of tissue The saccule is as a rule collapsed

In both sub-groups of genetically determined deafness PAS positive deposits of unknown significance are frequently found in the stria vascularis and within the epithelium of the macula sacculi.

The changes in the second sub-group show a strong resemblance to changes which originally were regarded as characteristic for a healed mild serous labyrinthitis, secondary to an infection of the middle ear or of the meninges However they were also experimentally produced by Wittmaack by introducing certain chemical substances, such as calcium chloride into the middle ear and letting them diffuse through the round window membrane into the fluids of the inner ear and called by him posthydropic neuroepithelial degeneration. Recently they have also been found in virus diseases of the inner ear particularly after maternal rubella in the first trimester of pregnancy In the absence of a well documented history the differentiation between these different types of changes sometimes becomes very difficult However in none of the so far reported cases f virus endolabyrinthitis have concrements in the stria vascularis or the macula sacculi been found or has a hydrops been demonstrated

The similarity between certain changes in cases of genetically determined deafness of the cochleosaccular type and those in healed serous labyrinthitis of a mild degree including cases of virus endolabyrinthitis, has for a long time been puzzling

It is well known that lesions brought about by the action of genes may be closely duplicated by a variety of unfavourable extrinsic factors (so-called phenocopies) The possibility therefore exists that in some cases of

congenital deafness where the hearing loss has no genetic basis, the loss may be due to an unfavourable enviromental factor. According to Bosher & Hallpike (1965) it would seem likely that in the course of the maturation process the endolymphatic system has to pass through certain critical phases. They in themselves are liable to constitute an unfavourable environment which in combination with an unfavourable gene might bring about a form of cochleo-saccular degeneration. It is conceivable that viral damage to the developing stria might act similarly to a "genetic weakness" interfering with the ability of the stria to maintain the normal chemical constitution of the endolymph in the developing cochlea.

An analysis of the histological findings in hydrops of the labyrinth, regardless of its cause, leads to the conclusion that one of the first changes is a disruption of the attachments of the tectorial membrane to the various parts of the organ of Corti with subsequent retraction of the membrane. The retraction and the change in the shape of the membrane on cross sections from bandlike to globular could be explained by the assumption that it is elastic and stretched over the organ of Corti and that possibly after the attachments are broken, the membrane shrinks and tends to achieve a shape with the smallest circumference. The retraction of the tectorial membrane might also facilitate penetration of the endolymph into the subtectorial space and into the spaces normally filled with "Corti-lymph". The mixing of the two fluids might cause degenerative changes in the organ of Corti, particularly in the hair cells.

The group with evident anatomical anomalies of the inner ear shows changes not only of the contents of the cochlear duct and of the saccule but also of the osseous framework of the cochlea. Siebenmann named these cases typus Mondini because they resemble the case first macroscopically described by Mondini (1791). In all of them both sides are affected. In the fully developed form the bony capsule of the cochlea is flattened from the base to the apex and the normal arrangement of the scalae is present only in the basal cochlear turn where the septum between the lower basal and middle turn is present. In the upper parts the interscalar septa are absent and a scala communis or cloaca is formed. The modiolus and the spiral laminae also show defects of varying degree. The cochlear turns are often reduced to 2 or even 1 ... the cochlear duct is in some instances markedly dilated, either along the entire course or in its upper parts only. In other cases the duct is collapsed. The saccule, the endolymphatic duct and sac are almost invariably, the utricle occasionally dilated. The membranous canals are as a rule normal. The organ of Corti is usually absent in part of the duct particularly in the more malformed upper region and is reduced to a flat mound of more or less undifferentiated cells in other parts. In some instances it shows typical "posthydropic" changes. The stria vascularis and the ligamentum spirale are often somewhat atrophic. Frequently the spiral ganglion presents a reduction in the number of the ganglionic cells and nerve fibers belonging to the more affected upper part ... in

rare instances it is completely absent In other cases the ganglion is situated in the central parts of the modiolus and in the fundus of the internal auditory meatus Changes in the primary cochlear nuclei were reported in some cases Although the majority of the changes are unquestionably the direct result of an abnormal development the "posthydropic" epithelial changes could have been brought about indirectly by the same mechanism as in the cases of the first group by a "genetic weakness of the stria vascularis which interfered with its ability to maintain the normal chemical composition of the endolymph in the developing cochlea The anomalies of the mesenchymal parts in these cases are probably to a certain extent dependent on the degree and nature of the malformations of the ectodermal parts It should, however be kept in mind that minor anomalies in the mesenchymal parts of the cochlea are often found in the absence of anomalies in the epithelial or nervous elements

RÉSUMÉ

Les observations d organes sensoriels en cas de surdité déterminée génétiquement se divisent en deux groupes. L un est caractérisé par des changements qui ressemblent à ceux que l on observe dans les labyrinthites séreuses ou virales guéries (rubéole maternelle) l autre dans une dégénérescence neuroépithéliale posthydropique bénigne Il y a des analogies entre les changements causés par les facteurs génétiques et par les facteurs extrinsèques. On peut considérer l hypothèse que tous ces changements pourraient être le résultat d un désordre de la strie vasculaire Ce désordre empêcherait de maintenir la composition chimique normale de l endolymphe

ZUSAMMENFASSUNG

Bei genetisch bedingter Taubheit können an den Endorganen zwei Arten von Befunden erhoben werden Die eine Art ähnelt den Befunden bei leichtgradiger seröser Labyrinthitis, bei Virus-Endolabyrinthitis (nach mütterlicher Rubella) oder bei leichtgradiger posthydropischer Neuroepithel Degeneration Die andere Art zeigt rein degenerativ atrophische Veränderungen die an die bei der genuinen Neuroepithel Degeneration erinnern *In Anbetracht der Ähnlichkeit der Befunde* bei genetisch bedingter und bei durch äussere Einflusse verursachter Taubheit wird die Möglichkeit in Betracht gezogen dass alle diese Veränderungen letzten Endes auf eine gestörte Funktion der Stria vascularis zuruckgeführt werden können *Die geschädigte Stria kann dann die normale* chemische Zusammensetzung der Endolymphe nicht mehr aufrechterhalten

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DISCUSSION

I Fri dmann I have enjoyed this classical but somewhat disturbing presentatio The limitations f morphology are well known and the difficulties, technical and interpret tive well known. Y t the morphologist must continue to try to demonstrate certain morpholog cal features and correlate them with th associated syndromes and possibly with the probable underlyi g causati e mech n m.

Demonstration of three section demonstrating PAS-positive deposit in the ascular stria f a child wh died sufferi g from the cardioauditory syndrome (Lange Nielsen and Ierwell, 1957 Friedmann Fraggatt & Fraser 1965, *J Laryngology*) Also Electro photograph of ffect of neomycin on macula f th guinea-p g (Friedmann Dodsw ll & Bird 1966, *J Pathology & Bacte iology*)

N Torok The hypothesi is that the ult mate cause of function los is the nvasion of ndolymph into the cortilymph, causing the loss f cochl ar func tion. H w can the vestibular function loss be explained? Most of the conditi n responsible for developmental or degenerative inner ea disease re causing sim la ly tot l paralyses of the est bular or the cochlea ystem.

F Altmann (Reply) t M *Friedmann* I did not mean t say that we will never be able t histologically differentiate arious types f disease entities. However I I not think that it i possible at the present time On the other h d the possibility ist that the inner ear reacts to variou intrin ic and xtrinsi st muli in an identical way The PAS-positive concrements are ery peculia because they has so fa only been found in genetically determined and ot n equ red deafness n explanation can be given f r it at th present time

to M *Torok* I m unable t gi n xplanation for a loss f estibular re-ponses in cert in cases f inherited deafness. The histological hange are usually conf ned t or much more marked in th pars inferior The physiology f the l byrinthine fluid I the pars supe ior is much les understood than that in the pars i ferior

rare instances it is completely absent In other cases the ganglion is situated in the central parts of the modiolus and in the fundus of the internal auditory meatus. Changes in the primary cochlear nuclei were reported in some cases Although the majority of the changes are unquestionably the direct result of an abnormal development, the "posthydropic" epithelial changes could have been brought about indirectly by the same mechanism as in the cases of the first group by a genetic weakness of the stria vascularis which interfered with its ability to maintain the normal chemical composition of the endolymph in the developing cochlea The anomalies of the mesenchymal parts in these cases are probably to a certain extent dependent on the degree and nature of the malformations of the ectodermal parts It should however be kept in mind that minor anomalies in the mesenchymal parts of the cochlea are often found in the absence of anomalies in the epithelial or nervous elements

RESUME

Les observations d organes sensoriels en cas de surdité déterminée génétiquement se divisent en deux groupes. L un est caractérisé par des changements qui ressemblent à ceux que l on observe dans les labyrinthites séreuses ou virales guéries (rubéole maternelle) l autre dans une dégénérescence neuroépithéliale *posthydropique bénigne Il y a des analogies entre les changements causés par les facteurs génétiques et par les facteurs extrinsèques.* On peut considérer l hypothèse que tous ces changements pourraient être le résultat d un désordre de la *strie vasculaire* Ce désordre empêcherait de maintenir la *composition chimique* normale de l endolymphe

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MATERIALS AND METHODS

Experiment I Effect of Sodium Fluoride on Tissue and Organ Cultures of Human Otosclerotic Bone

Surgical specimens of otosclerotic bone were each divided in two pieces one always being a control, the other being cultured with sodium fluoride.

Some of these pieces were put into standard Rose chambers under tissue culture conditions with a media consisting of 85% Medium 199 and 15% Calf Serum Time lapse studies were done on these

Organ culture conditions were produced for the other specimens by (1) Rose chambers modified by the use of cellophane strips on both sides of the specimen, and (2) Roller tubes. Two media were employed the first being the same as that used for tissue culture the second being the media described by Biggers *et al* (1961)

Sodium fluoride in strengths of 1 to 15 ppm was used in the media for one half f each specimen Tetracycline HCl (5 10, or 25 µg/ml) was put in all the media.

Experiment II Effect of Sodium Fluoride on Heparin induced Osteoporosis

Sprague-Dawley strain of rats were used, each litter with their nursing moth r compri ing one test Each litter of 8 (or a comparable number) was divided into tw groups 4 babies who received sodium fluoride in some form from birth and 4 wh did not The first 4 received daily intraperitoneal injections of 0 002 mg sodium fluoride for the three weeks prior to weaning for the next ix weeks they received 10 ppm sodium fluoride in their drinking water At the age of 9 weeks each of the groups was further subdivided, half of ea h recei ing heparin (Liquamin Sodium) subcutaneously three times daily for a total of 400 units per day for four weeks. The ther half did not receive it. This now gave u four groups

A Control
B Heparin
C Sodium fluoride
D Heparin and sodium fluoride

During the period f nursing, the mother wa injected intraperitoneally daily with 3 mg tetracy line After weaning, the babies all got 1.5 mg each in the sam way Thirteen weeks after birth the experiment wa terminated. When using heparin, special care had t be tak n of the animal because f the risk of bleeding

Cal aria, humerus, radius, ulna, femur tibia, and fibula were di sected

The authors gr t f lly thank Dr Georg G. Rose for thi modification suggested t Dr Petrovic d ring personal t lk

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STUDIES OF SODIUM FLUORIDE EFFECTS

(a) On Human Otosclerotic Bone
(b) On Prevention of Experimental Osteoporosis in Rats
(c) Synergistic Action with Phosphates

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In newborn rats, NaF in optimal doses promotes bone calcification both by decreasing bone resorption and stimulating calcium deposition. Sodium fluoride also has a preventive action on heparine-induced, cortisone-induced and fracture-induced osteoporosis in 6- to 8-week-old rats, especially if given both before and after experimental fracture and combined after fracture with Na_2HPO_4 and KH_2PO_4. Both the above results were observed by the semi-quantitative evaluation of tetracycline labeling vs. microchemical calcium assays.

INTRODUCTION

Long term administration of large doses of heparin (Griffith *et al.* 1965) and of cortisone (Stahl & Gwestner 1960, Goldsmith & Stahl 1953) have been shown to bring about osteoporosis.

On the other side clinical studies have suggested that sodium fluoride might have a beneficial effect in bone resorptive diseases such as osteoporosis (Rich & Ensick, 1961) and Paget's disease (Purves, 1962). Clinical studies have also indicated that phosphatesupplemented patients with fractures had an attenuated demineralization in the immobilized limb as compared to the non supplemented patients (Goldsmith *et al.*, 1967).

This paper concerns the effect of sodium fluoride on human otosclerotic bone in organ culture and the prevention of heparin and cortisone induced osteoporosis in rats. *The synergistic action of sodium fluoride and certain* phosphates will also be considered as well as their possible use for the active otoporotic stage of the disease process known as otosclerosis. It will be presented in three parts:

1. Materials and methods.
2. Experimental results.
3. Discussion.

This work was supported by Grant 5 R01 NB 02874 from the Public Health Service, National Institute of Neurological Diseases and Blindness, NIH.

peared early and was very exuberant Its fibroblast like cells ranging from 30 to 80 μ The more mature lesion produced a less intense outgrowth with smaller (25 to 45 μ) osteoblast-like cells. The latter were round in shape, with eccentric nuclei, and high Alkaline Phosphatase content Time-lapse photography of the cells of both types of outgrowths showed the char acteristic movements of their representation

When these outgrowths were treated with sodium fluoride, we could not detect any significant effect. But with concentrations of sodium fluoride *up to 15 ppm no deleterious effect on human otosclerotic cell growth* and proliferation or on the cytoplasmic movements (as analyzed by time-lapse microcinematography) were detected either

Our next step was an attempt at growing the otosclerotic surgical speci m ns under organ culture conditions. Each specimen was divided in two, with tetracycline given to both to detect new bone formation by a char acteristic fluorescence under ultraviolet light The medium of only one half of each piece contained sodium fluoride in order to detect its effects n calcification. Figs. 1 and 2 show two halves of a surgical specimen of tosclerotic bone Tetracycline fluorescence is both more intense and spread over a wider area in the half with sodium fluoride This means that in organ culture sodium fluoride *does* have a promoting effect on calcification of tosclerotic bone

Experiment II Effect of Sodium Fluoride on Heparin-Induced Oste porosis

Between groups A (control) and C (sodium fluoride) there was no signif icant difference in UV-induced fluorescent intensity (see Fig 3) *C* was possibly brighter than A, but only marginally In those bones treated with heparin, group B (heparin alone) was much lighter than D (heparin with sodium fluoride) If these groups were placed in a line of decreasing in ten ity the order w uld be as follows C–A–D–B

From our previ u research on rats we have found that tetracycline is deposited at the same time as the calcium of bone f rmed during its ad m nistration *Th more calcium deposited* the more tetracycline also deposited and theref re the greater fluorescent intensity Thi has been double-checked by microchemical spectrophotometric assays of calcium Petrovic *et al* 1966) The validity of a semi-quantitative estimation of cal ium deposition wa confirmed by studies of endochondral ossification of the anterior extremity of Meckel cartilage (Petrovic & Shambaugh, 1966 Petrovi *et l* 1966)

In the light f thi previou study we can interpret our results to see that group B (heparin, but no sodium fluoride) had th least amount of cal ium c mpared to the group getting no heparin. Group D (heparin nd s dium fluoride) lso had a lower amount, but not a small as that of B F om this we can see that the difference in fluorescent intensity is greater

and divested of all non bony material They were then photographed under ultraviolet light in the following pattern for an easy comparability

		Heparin	
		No	Yes
Sodium fluoride	No	A	B
	Yes	C	C

Ten litters were thus examined

The method of photography was the same as that detailed in a previous paper (Petrovic & Shambaugh 1966)

Experiment III Effect of Sodium Fluoride and Sodium Phosphate dibasic (Na_2HPO_4) and Potassium Phosphate monobasic (KH_2PO_4) on Cortisone induced Osteoporosis

Sprague Dawley rats were again used and tetracycline given as in the heparin experiments Twelve litters were examined

The chart below details the time and dosage of sodium fluoride cortisone acetate and phosphates given to litters of 12 rats. There are six groups within each litter each group consisting of 2 rats. The first group is a control group receiving only tetracycline

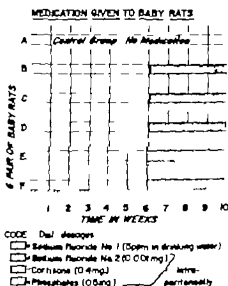


Fig 1 Hum t sel rotl footpl te c ltured with t t ycll f 5 da s.

Experimental Results

Experiment I Effect of Sodium Fluoride on Tissue and Organ Cultures of Human Otosclerotic Bone

We found with the tissue culture methods that normal stapes footplate did not give rise to any signif cant cell outgrowth, but the otosclerotic foot plate did When the lesion was immature and active, the outgrowth ap-

peared early and was very exuberant. Its fibroblast like cells ranging from 30 to 80 μ. The more mature lesion produced a less intense outgrowth with smaller (25 to 45 μ) osteoblast-like cells. The latter were round in shape with eccentric nuclei, and high Alkaline Phosphatase content. Time-lapse photography of the cells of both types of outgrowths showed the characteristic movements of their representation.

When these outgrowths were treated with sodium fluoride, we could not detect any significant effect. But with concentrations of sodium fluoride up to 15 ppm no *deleterious* effect on human otosclerotic cell growth and proliferation or on the cytoplasmic movements (as analyzed by time-lapse microcinematography) were detected either.

Our next step was an attempt at growing the otosclerotic surgical specimen under organ culture conditions. Each specimen was divided in two, with tetracycline given to both to detect new bone formation by a characteristic fluorescence under ultraviolet light. The medium of only one half of each piece contained sodium fluoride in order to detect its effects on calcification. Figs. 1 and 2 show two halves of a surgical specimen of otosclerotic bone. Tetracycline fluorescence is both more intense and spread over a wider area in the half with sodium fluoride. This means that in organ culture sodium fluoride *does* have a promoting effect on calcification of otosclerotic bone.

Experiment II. Effect of Sodium Fluoride on Heparin Induced Osteoporosis

Between groups A (control) and C (sodium fluoride) there was no significant difference in UV induced fluorescent intensity (see Fig. 3). C was possibly brighter than A, but only marginally. In those bones treated with heparin, group B (heparin alone) was much lighter than D (heparin with sodium fluoride). If these groups were placed in a line of decreasing intensity, the order would be as follows: C–A–D–B.

From our previous research on rats we have found that tetracycline is deposited at the same time as the calcium of bone formed during its administration. The more calcium deposited, the more tetracycline also deposited, and therefore the greater fluorescent intensity. This has been double-checked by microchemical spectrophotometric assays of calcium (Petrovic *et al.* 1966). The validity of a semi-quantitative estimation of calcium deposition was confirmed by studies of endochondral ossification of the anterior extremity of Meckel's cartilage (Petrovic & Shambaugh, 1966; Petrovic *et al.* 1966).

In the light of this previous study we can interpret our results to see that group B (heparin, but no sodium fluoride) had the least amount of calcium compared to the group getting no heparin. Group D (heparin and sodium fluoride) also had a lower amount, but not as small as that of B. From this we can see that the difference in fluorescent intensity is greater

between non heparin and heparin treated bones when they had received *no* accompanying sodium fluoride than when sodium fluoride was given. In this case the difference between heparin and non heparin treated bones was less, indicating that sodium fluoride had in some way significantly hindered the osteoporotic effect.

We went one step further and checked the parathyroids of the animals treated in this experiment Goldhaber (1965) has shown that in tissue culture heparin enhances the amount of bone resorption obtained with parathyroid extract or other factors which stimulate bone resorption We want to emphasize that our cytological and cytochemical study of the para thyroid did not lead to the detection of any stimulation of parathyroid by the use of heparin In other words, the action of heparin on bone seems not to be mediated through the parathyroids

Experiment III Effect of Sodium Fluoride and Sodium Phosphate dibasic (Na_2HPO_4) and Potassium Phosphate monobasic (KH_2PO_4) on Cortisone induced Osteoporosis

The UV induced tetracycline fluorescence seen in the bones of the litter *mate rats grouped from A to F (see above—Materials and Methods)* permit

FIG. 2. Portion of same footplat Fig 1 cultured with t tracycline and 5 parts per milli n of sodium fluoride in th culture medium The much greate fl rescence in Fig 2 indicates greate alcium depositi n duri g 8 days of culture s a result f sodium flu ide eith r promoting cal i m d position or red ci g resorpti a combination

FIG 3 Tibia nd fibula f rat littermates that received th foll wing (*a*) Upper left, n xt t cross, control receiving tetracyclin only from th 1st t th 13th week fter birth (*b*) Upper right, litte mate rat receiving tetra ycline 1st through th 9th week, tetracycli e and 400 units of h parin daily 10th to th 13th week, h wing heparin-induced osteoporo i ( ) Low r l ft, rat receiving tetra clin 1st to the 3rd week, tetracycline a d 10 part pe milli n f sodium fluoride i drinki g water 4th t the 13th week, (*d*) Low right, rat receiving tetracycli 1 t to 13th week, with sodi m flu id in th drinking wat r 4th t 3 th week, h pa in, 400 unit dail 10th t 13th week, showi g protection gai st h parin induced steoporosis result f sodium flu ide

FIG. 4 Leg bo es f rat littermates (*a*) Upper left rat ec i ing tetra li nly 1st through 10th week (*b*) Middl l ft, rat recei i g t tracyclin plu 0 4 mg cort so from 7th to 10th week, h wing corti e-i duced osteoporosi ( ) Lower l ft sam medica ti n but with 0.5 mg pho phates dded 7th t 10th week, showi g steoporo not ignificantly red ced by phosph tes i (*d*) Upper right, rat recei ing tetra li 1st to 10th week, with corti n 0 4 mg d 5 part per n ll odi m fl rid i drinking wat added th to 10th week. Slight protecti gainst cortiso nduced osteoporo is compared t (*b*) ( ) *Middle right rat recei ing t tra line 1 t t 10th* week, with cortison sodium flu rid and phosph tes dded 7th to 10th week, h wi g reduced cortiso induced osteoporosi (*f*) Low ight, same periment ( ) b t with sodium fl rid dded t th dri ki g w t 4th to 6th week pr t dmi teri g corti one Here the maximum protect gai t corti d ced teoporos m ee with no difference in th fluorescence mpared to control f (*a*)






the following relationships. Osteoporosis is blatently evident in group B its calcium content is enormously diminished from the amount seen in the control group A. There was no observable significant difference between the bones of B (cortisone) and C (cortisone and phosphates simultaneously) B and C both show the least amount of fluorescence, i.e. the least amount of calcium The osteoporosis of B was not significantly hindered by the addition of phosphates alone as seen in C. A slightly greater calcification was evident in D (cortisone and sodium fluoride simultaneously) but w have seen before that sodium fluoride promotes calcification, so this would be expected When in E, phosphates, sodium fluoride, and cortisone were all given at the same time even more calcification was evident by another increase in fluorescence Since phosphates alone seem to produce no detectable effect, a synergistic action between sodium fluoride and phosphates seems to be indicated. The optimum conditions to prevent cortisone induced osteoporosis are evident in group F where sodium fluoride was given before cortisone and then sodium fluoride cortisone and phosphates were given simultaneously That this interaction *was* the optimum can be ea ily seen when group F shows the same amount of fluorescence as A—the control Timing the treatment thus completely negated the osteoporotic effect f cortisone Calcium deposition occurred at the same rate as in the untreated control and there was no significant increase in resorption. We must mention that even under rigorous experimental conditions, we often observed some quantitative differences from litter to litter

Experiments now under way confirm that the best way to hinder and at time actually prevent osteoporosis, is to administer the sodium fluoride f r prolonged periods *before* the heparin intake and then to give sodium fluoride with phosphates *afterward*

DISCUSSION

First, we would like t emphasize the following methodological point W do *not* state that the differences in the fluorescent intensity of tetra cy l ne result exclusively from the differences in the deposited calcium amount other fact rs may be causative But, our previou experiment h shown that when there i intense bone depositing activity—either lone r c mbined with bone remodelling—then the great diff rences in fluorescent intensity *do* relate t the amounts of calcium deposited.

The alidity f the tetracycline labeling method was in fact upheld when n n ea lier paper (Petrovic *et al* 1960) we howed that when there is mor calcium, there i a higher fluorescent intensity We knew that tetra cy l ne wa good f r a semi-quantitati ev luation of calcium amounts, but w w nted a microchemical analysi by a spectrophotometric method f th exact amount of calcium present in the bones after vari u sodium fluoride doses. The f r such a study wa done on newborn rat parietal

bones and the results have shown a definite corroboration of sodium fluoride's promoting effect on deposited calcium (Petrovic & Shambaugh, 1966) A marked difference in effect is seen between the two doses the strong dose does not give as good an effect as does the optimal This relates exactly to the differences in tetracycline fluorescence

As tetracycline was given from the beginning to the end of the experiments reported in this paper we do not know what part is due to deposition and what part is due to resorption—but we do know the overall result This was done purposely in an effort to reproduce in animals the human clinical situation

As used in our experiments, the technique employed appears valid in which case our results, as reported above show that sodium fluoride may hinder or entirely prevent heparin or cortisone induced osteoporosis

The problem then arises What are the possible mechanisms involved in this sodium fluoride action? We do not here wish to discuss this important problem at length However we will mention two of our previous experiments which give some insight into the possible mechanisms involved

Our previous investigations (Petrovic & Shambaugh, 1966 Petrovic *et al* 1966) have shown that sodium fluoride certainly brings about a reduction in bone resorption and most likely brings about a promotion in bone calcification To analyze this further we did an organ culture study of previously sodium fluoride-enriched bone specifically checking the osteoclasts after parathormone-induced resorption (Petrovic *et al* 1967) Tetracycline fluorescence showed us that the bone trabeculae with a higher sodium fluoride *content underwent a less intense parathormone induced resorption* Radioautographic studies using H^3-cytidine and H^3 leucine incorporation showed that the osteoclasts seem to have a lower functional activity when the bone trabeculae undergoing resorption had a higher fluoride content This lessening of osteoclastic functional activity could be a result of either a decreased proneness of the sodium fluoride richer bone trabeculae to be resorbed *or* an increased localized concentration of fluoride consecutive to the local release of fluoride during bone resorption Of course it could be a result of both

A new series of organ culture experiments was set up to find out whether there was an action on calcium deposition itself For this we studied the incorporation of Ca^{45} into the 18-day-old mouse embryonic ulna, both with normal and sodium fluoride-plus media Results clearly show that the amount of Ca^{45} *incorporated in organ culture into the ulnas was significantly* higher when sodium fluoride was added to the medium These experiments were designed specifically to see whether there is stimulation of Ca^{45} uptake from sodium fluoride We realize that even in embryonic bone *resorption* may be occuring In any difference of Ca^{45} between treated and untreated explants we cannot exclude the possibility of resorption occuring simultaneously with deposition However because of the very short term of the experiments and the embryonic age of the specimens used, we believe

we can safely conclude that the bulk of the difference must be due to an increased calcium deposition. What is irrefutable is that the total amount of incorporated Ca^{45} has been increased, whatever the mechanism.

One last word related to heparin induced bone resorption concerns investigations now in progress on hibernators. We have observed that those bones undergoing, during the winter sleep, a more intense resorption contain at the same time more mastzellen cells known to secrete heparin.

CONCLUSIONS

1. In tissue culture normal stapes produce no significant cell outgrowth; young active otosclerotic stapes produce an exuberant, fibroblast like outgrowth; mature otosclerotic lesions produce a less intense, more osteoblast like outgrowth. Concentrations of sodium fluoride up to 15 ppm have no deleterious effect on the cell growth or proliferation.

2. In organ culture sodium fluoride has a promoting effect on otosclerotic bone calcification.

3. In young rats, sodium fluoride definitely prevents experimental osteoporosis, whether this was induced by heparin or cortisone, as reported above, or by fracture as reported in a previous paper.

4. When cert in phosphates (Na HPO and KH PO) are associated with sodium fluoride a synergistic action produces a much better prevention of osteoporo i than either alone as seen by the experiment with cortisone.

5. From our experiment it appears that the best way to hinder and even prevent osteoporosis is to administer the sodium fluoride in small amounts for prol nged periods bef re heparin or cortisone intake or fracture, and then t gi e sodium fluoride with phosphates (Na_2HPO_4 and KH_2PO) fterwards.

6. What i essential i that the optimal dosage be found for each species, ge and indi idual (as we have done f r one strain of rat) to gain the f rable ffect. Too high a concentration of sodium fluoride will have a deleteriou effect on bone calcification. Often it is advisable to lengthen the t me of treatment rather th n strengthen the dosage.

7. These experimental findings strongly suggest that sodium fluoride along with phosphates might be useful in the treatment of patients with secondary osteopor sis, Paget disease and—perhaps—the otoporotic stage of tosclerosis.

ACKNOWLEDGMENTS

Th uthors gratef lly acknowledge M Sheila Chilton for her as istance. Mrs. Kathleen M rinolti for th histological work, and M J mes Alexander for the phot graphy.

RESUME

Chez le rat nouveau né le NaF en doses optimales favorise la calcification osseuse en entraînant à la fois une diminution de la résorption et une augmentation du dépot calcique D autre part chez des rats de 6 à 8 semaines, le NaF prévient l ostéoporose consécutive à la fracture surtout si on l administre avant et après la fracture expérimentale et qu on l associe après fracture aux Na_2HPO_4 et KH_2PO_4 Ces résultats furent obtenus grâce à une évaluation semi-quantitative au moyen de la tétracycline ainsi que par le microdosage du calcium.

ZUSAMMENFASSUNG

Optimale Dosen von NaF fördern die Knochenkalcification in neugeborenen Ratten durch die Verminderung der Knochenresorption und durch Förderung der Kalziumablagerung NaF verhindert ebenfalls durch Fraktur herbeigeführte Osteoporosis in 6–8 Wochen alten Ratten besonders wenn vor und nach experimenteller Fraktur verabreicht und nach Fraktur kombiniert mit Na_2HPO_4 und KH_2PO_4 Beide Resultate wurden durch semiquantitative Auswertung von tetrazykliner Markierung versus mikrochemische Kalziumbestimmung beobachtet

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G F Shambaugh J M D
Dept f Ot laryng logy N rthwest n
University M dical School Chicag
Ill U S A

DISCUSSION

J M Tat Your e perimental studies re very promising and support in some w y the use f N F and phosphates in tosclerosis, Paget Recklinghausen nd osteogen is imperfecta. W learn that it is necessary to use optimal doses. I want t sk the uthors which are these optimal doses for otosclerosi and the other osteodistrophies.

G Kelemen Observation of cat with the inevitable nasal and paranasal suppural e condition undergoing imilar medication might add results of practical portent.

G Shambaugh (Reply) The exa t eti logy of loc lized osteoporosi of the labyri thin capsule (misnamed otosclerosis) i not known. The two diseases are not directly a sociated, but th re are simil rities. Both re m re frequent in f males than in males preg n y an l the men pause are predisposing f ctors w i le l ered ty pla a part The demonstratio by Dr Petro ic s beautifully con trolled xperiment that the generall ed osteoporosis i luced by cortison r heparin and the localized osteoporosis t th t of fra ture can both be inhibited by sodi m fluor de encourages u to h pe that localised osteoporos at the laby inthine psule may be influenced in the same manne

Our experiences up t d t are little encouraging, but t th same time a little d scouraging (lide)

E periment now under way in ur laborat ry indic t that the osteoporotic h b t g ffect of sod um fluoride is con id rably strengthened b gi ng ph sphates t th same t me Th w re now starting t use n ur patients with p lyt mograp ic demo stration of acti porosis f the laby inthine capsule f ome t two years w will ha e suff cient data t k ow whether there is a r ler t rarable ffect on the cti st ge f ot sclerosi tha with sodium fluor i alon

The d sage f these medication i a follows

S d u f uor le 20 m gm teri tw ce daily

H perphos K (Rose Da es Co) t thre times da ly

Until cont ued for 1 ea Repeat polytomography 6 month after the last dose

Dosage critical	*Length f administration*
20 mg. too little	3 months, too short
150 mg. t o much.	6 months, better
60 mg. about ght	1 year st ll better
40 mg. about ght an l phosph tes.	

Mech phase of remodelling process.

Cawthorn N ghtmare

Effect t pes f xat on on coct lear oto, on hist logic ot

D Petrovic (Rep ly) I wish t tha k M K l m n f r hi very interesting suggest on M Shambaugh ha lrea l an wered M Tat question I just t t ad l that although w cannot xtrapolat lirectly from mal t man as r rd oses f sod um fluorid a d phosphates, w ha found that if the ba f comparison i the bod we ght, the rat requires more sodi m fluoride f r promo tion of bon calcification th n huma but if th basis for compa ison is th calcul ted body rfa then the rat a d m n re in th same range f lues, not forgetting ind idual differences f course

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LIPOID MATERIALS IN THE COCHLEAR DUCT OF THE GUINEA PIG

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A cord of highly refrangible materials in the external spiral sulcus of the guinea pig's cochlear duct is described It is present in all the cochlea s turns except the basal turn The materials are positive to Sudan III and Sudan Black, and are dissolved in alcohol and ether With the same approach research is performed on other species white mouse rabbit cat and man

INTRODUCTION

While performing dissections on the guinea pig s cochlea, we were surprised to find a material in the form of a cord, highly refrangible floating easily in the watery medium and separating itself when the lamina was removed and placed in fresh material The frequency of the findings completed us to investigate its localization and origin or try to identify it with some known elements of the cochlear duct

METHODOLOGY

Fifty guinea pigs were used, varying in weight from 70 to 000 g each. *Sodium pentothal by the intra abdominal procedure was used as an* anesthetic Dissection was performed with the retroauriclo technique until the auditive bulla was localized Using a dissection microscope, the bony lamina was separated from the cochlea s turns It was possible to keep the labyrinth s membranous part in place

Using an 11 B P scalpel the modiolus was transversally cut at the level of each cochlea s turn The cuts were studied separately

FINDINGS

It was possible to observe in the angle formed by the basilar membrane and the spiral ligament a cord of granular aspect highly refrangible and localized on the three superior turns, but in every case it was absent in the basal turn The cord separates easily and tends to float Its average thickness was 102 (microns) (Figs 1 and 2)

This cord, observed *in vivo* or fixed in formaldehyde in phase contrast, is formed by numerous circular drops the largest being 10 or 12 The

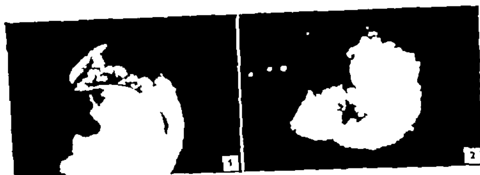


FIG. 1. G tnea pig cochlear Lipid cord *in sit*

FIG. 2. Cord f gra lar pect, floati g.

small ones are hardly visible with 1900 diameter Under the drops, and difficult to see we found polygonal cells, placed next to each other very similar and with a small round and central nucleus (Fig 3) The cytoplasm, with a slightly dense aspect, presents profuse chondriome and a rod-shaped chondriosome (Fig 4) Accurate observation of these materials suggests, for the small drops, an intra-cellular localization, while for the larger drops, an extra-cellular localization

The drops were quickly dissolved by alcohol and ether while observation w s being carried out under the microscope Nevertheless, no space appeared between the cells. The latter suggests that the larger drops were on top of the smaller ones, and not between them. To kn w more about its h mical composition, the following techniques were used for general lipids, Sudan III and Sudan Black (MacManus & Mowry 1960) Smith s method (1908) modified by Cain (1947) showed us the neutral and acid lipids. Smith & Mair s technique, with Blue Nile, showed the phospholipids and the acid lipids. A method for identifying cholesterol was used, too, and hematoxylin-eosine as a rutinary method The material was positive to all lipid techniques and always negati e to cholesterol technique

The liquid used to receive the material was Dulbecco s, but modified by us in its proportions of Na (Sodium) and K (Potassium) We increased the l tter and decreased the former This liquid was more isot nic f r the cells of the cochlear du t than any ther saline solution previously recommended for diverse ti sue Nevertheless, since cellular swelling was observed, other liquids were used, too, such as Ringer s, Tyrode s and Gey s. Gey's was the best from the tonic point of view

When, duri g dissection, the organ of Corti separates violently from the spiral ligament, u ually the lipoid cord remains adhere to the external region of the organ of Corti. For this reason, we consider the cell that make up the lipoid cord to be cells of the external spiral ulcus. (Fig. 5)

Th next step in our research was ear dissections on newly born guinea pigs. W f und the lipoid cord in the same place and more or less with the

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LIPOID MATERIALS IN THE COCHLEAR DUCT OF THE GUINEA PIG

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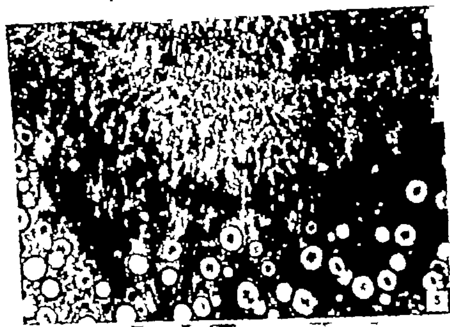




Fig. 5 Orga of Corti Cells of the external piral lcus.

Fig. 6. "Grumes or lo((the cat spiral ligament

tainly were not as abundant as in the guinea pig. (Fig. 6) In the rabbit nd white mouse no lipid material was found in their cochlear ducts. In the human temporals, n material similar to the guinea pig's lipid cord wa identified. Using Sudan III and Sudan Black, fragments of the spiral ligam nt and the organ of Corti were tested The results were negative

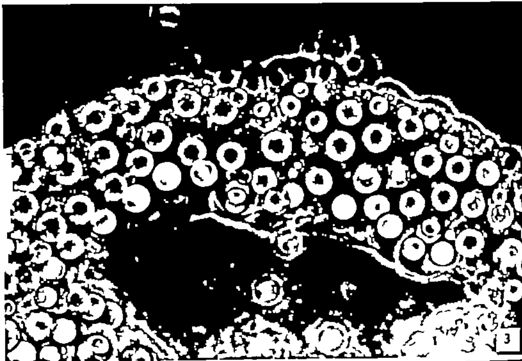




FIG 3 P l g n l ll with th l rou d nd ce tral l

F 4 C t pl m with h dri me, nd rod haped h dri m

same dimensions as in the adult guinea pig We continued the investigation on other species cats, rabbits, white mice and some human temporals fixed in formaldehyde

In the spiral ligament and more specifically in the cat s vascular stria, we found a few small grumes or clots, which were positive to Sudan III and Sudan Black, but he former did not have the shape of a drop and cer

4. In the cat's vascular stria were found small grumes or clots positive to Sudan III, but not a lipoid cord. In the rabbit, white mouse and man, nothing similar was found.

5. It is suggested that the cells of the external spiral sulcus are the origin of the lipid drops.

RESUME

Une corde à matériel lipoïde est découverte dan le ca al cochléaire du cobaye. Elle est formée par des substances grasses sur des cellules polygonales. Elles donnent un réaction positive Sud n III au Sudan oir et au Smith Mair et une réaction négat u holestérol. Elle se dissout dans l' lcool et dan l'éther. Des tudes sont menées, dans le même but, sur des temporaux d'hommes, de hats et de rat blancs.

ZUSAMMENFASSUNG

Eine Schnur gebildet us Fettstoffen über polygonalen Zellen findet man in der Canalis cochlearis des Meerschweinchens. Die Reaktion uf Sudan III schwarzem Sudan und Smith Mair ist positi die auf Cholesterin negativ und löst sich in Alk hol und Äther auf. Ausserdem werden Studien zugl ichen Zwecken an menschlichen Schlafenbeinen und Schläfenbeinen von Katz n nd weissen Ratten erwähnt.

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DISCUSSION

In the bibliography studied on the organ of Corti including old and new reports and with various techniques, no reference is found to these peculiar structures (Ballenger & Ballenger 1938 Beaunis & Bochard, 1873 Besold & Siebenmann, 1908) The only reference mentions Hensen's cells as having inclusions of lipid material (Maximov & Bloom 1952 Tonndorf 1962)

No doubt the main factor is that histological techniques use ether and alcohols for dehydratation and embedding and these substances dissolve most of the lipid materials The possibility of confusing the lipid cord with some other structure of the organ of Corti such as, for instance the tectorial membrane that separates in the shape of a transparent ribbon was ruled out because both were easily obtained in the same samples

We think that the origin of this material might be the cells of the external portion of the basilar membrane, whose abundant chondriome is suggestive of high metabolic processes We can deduce, therefore, that we are not dealing with fatty tissue in the strict sense of the word, since in fatty tissue the intracellular fat increases with the gradual displacement of the cellular structures, pushing the cytoplasm towards the periphery of the cell and causing its death

In our material all the cells look alike and complete Their containing drops are very small giving the impression that the lipids soon become extra-cellular and coalescence to a certain limit, since drops or spaces too large were never found There is a remote possibility of the lipids being elaborated in another zone and clustered on the external spiral sulcus. But up to now we have not seen them dispersed or in another region of the cochlear duct

In the same way we can discard the idea of lipophanerosis phenomena following cellular death, because in the guinea pig we have observed the lipid drops while the cells underneath are still alive

In human beings, we tried to confirm Del Bo's findings (1957) He insists that positive Sudan Black materials are present in the inner hair cells of the organ of Corti and in the vascular stria In spite of the modifications and variants applied to this technique, we obtained only negative results.

CONCLUSIONS

1 A cord of lipoid material in the external spiral sulcus of the guinea pig's cochlear duct is described

2 It is formed by drops of lipid materials on polygonal cells having abundant chondriome

3 The drops reacted positively to Sudan III Sudan Black and Smith & Mair's phospholipids, and negatively to cholesterol Alcohol and ether dissolve the drops

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STATISTICAL EVALUATION OF HEARING LOSSES IN MILITARY PILOTS

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Regression analysis is a valuable statistical technique for following the evolution of hearing-loss over the course of time in acoustically traumatized subjects. On the basis of 786 audiograms of 673 Swiss military pilots, it was found that aging is the most significant factor influencing the threshold shift of the test group. In accordance with the relative acoustical characteristics of the flight noise patterns, propeller craft seem to cause more damage to hearing than do jets. By considering the standard deviation from the regression curves, single flyers may be selected out in order to get more information about their individual sensitivities to noise damage.

Many problems of noise-induced hearing loss have been solved during the last decade but, among others, an essential question has not yet been adequately answered. How much of an individual's threshold shift is really noise-induced and how much is due to aging?

The permanent threshold shift caused by the daily influence of industrial high-intensity noise seems to be established after 10–15 years of exposure (Glorig & Davis, 1961; Nixon & Glorig, 1961; Wagemann & Ahlborn, 1965). A further diminution of hearing therefore would be the consequence of aging. As threshold shifts due to noise and presbycusis are essentially different phenomena, they theoretically can be separated from each other by simple subtraction. Rosen's audiological and medical examinations of an African tribe threw new light on presbycusis (Rosen & Olin, 1965). He showed that in the phenomenon of presbycusis overall human aging plays a greater role than exposure to the noises of civilized life.

Most of the publications on noise-induced threshold shift deal with industrial and experimental noise sources of damaging intensity. Under these circumstances, individual sensitivity is of minor importance. Any individual exposed to such an intensity of noise over a certain period of time will be damaged sooner or later. However, susceptibility to noise varies among individuals and the susceptibility of a given individual probably fluctuates over time. From a prophylactic point of view, people whose hearing loss develops under less traumatizing circumstances need our special attention. Preceding experiments (Beck & Beickert, 1958; Sato, 1958; v. Schulthess,

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DISCUSSION

G Kelemen It is encouraging to hear about investigations regarding the pathology of diseases of the lipid group with their slowly accumulating clinical importance in otolaryngology

TABLE 1 *Statistical evaluation of hearing loss in military pilots.*

N = 673 pilots; 5786 audiograms.

Questionnaire
Pilot
Age
Noise protection during flight
Threshold shift for
500 cps, rt./lt. ear
1000 cps, rt./lt. ear
2000 cps, rt./lt. ear
4000 cps, rt./lt. ear
8000 cps, rt./lt. ear
Family history of hearing deficiency
History of illness
Non military noise exposure
Aircraft type
Propeller/jet helicopter
flying time (time of exposure)
Hearing test
Audiometer types (1 2 3 4)

overlapping of the c ndition demonstrated in Fig 1 makes a statistical study necessary

This report deals with the case histories of 673 pilots. These flyers had a total of 3786 bilateral threshold audiograms, which were computed in the Swiss Federal Statistical Bureau

A purely statistical program was used to follow the evolution of the threshold shift f the wh le group The regressi n curves and their standard deviations w re calculated On the basis of these statistical findings the pil ts whose hearing-loss exceed the standard deviation will be selected for further study Indi idual examinations of these pilots will be carried out this tudy may throw light on the reason for thei hearing-deficiencies, i.e. their sensitivity t noise damage This paper deals with the purely statistical part f th program whereas the second project is going on at th moment.

METHOD

The age of the pilot the threshold hift t various frequencies and dates, nd the flying time are li ted in the questionnaire example. Three types of ircraft (propeller jet and helicopter) are con idered (T ble 1)

W are indebted t M C Isard for ha ing collected the relevant data.

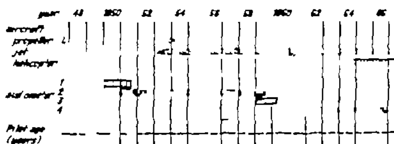


Fig 1

1961) have proved that, in the presence of subtoxic application of streptomycin or hypoxemia, a threshold shift can be produced by a noise which otherwise would be harmless.

This study attempts to approach the problem of these minor noise-induced threshold shifts by following the audiograms of a group of subjects over a certain period of time A regression analysis permits a determination of the rate of diminution of the hearing in the group with aging and under the influence of certain traumatizing effects.

MATERIAL

The effect of aging and exposure to flight noise in aircraft pilots was investigated Swiss pilots are submitted to training flights every year Auditory threshold tests are administered at regular intervals Flying time is registered and the physical characteristics of the noise in the aircraft as well as the effect of noise protective measures are known (Fig 1) The

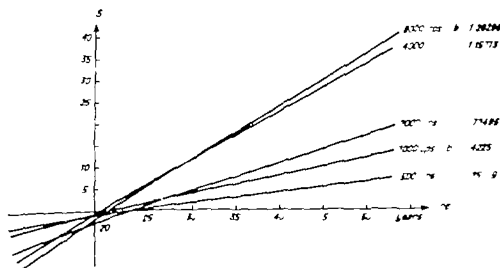


Fig 2

TABLE 2 *Thresholds shifts (dB) at 40 years of age*

	cps	500	1000	2000	4000	8000
Present study	Rt. ear	1.50	8.20	11.20	23.82	21.82
(flying staff)	Lt. ear	1.67	8.37	12.8	25.19	25.3
Other authors						
[illegible] (1953)		~7	~	~9	~12	~11
Glorig et al. (1954), Wisconsin Stat. Fair						
	Rt. ear	1.0	4.1	5.1	18.8	
	Lt. ear	1.6	4.8	6.2	21.5	
Amer. Stand. Ass. (1954)					~12	
Corso (1959)					~17	
Glorig (1961)			~3	~2	~12	
Hinchcliffe (1959)		1.7	1.7	2.6	8.3	3
AE (aging effect)						
Nixon & Glorig				1.38	7.6	

(c) Threshold shifts in the present study can be compared with the results of other authors. It is evident that in the present study there is a more remarkable threshold shift, especially in higher frequencies, than in other more or less selected groups (Table 2). This may be the consequence of other traumatizing agents, e.g. blunt trauma, exposure to industrial noise etc.

2. *The Relation of Threshold Shift to Flying Time*

This correlation, too, can be demonstrated by regression curves. From these data the following conclusions can be drawn.

(a) Aging and other eventual uncontrolled damaging factors have a greater influence on threshold shift than exposure to aircraft noise during flying time.

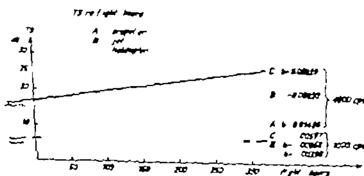


FIG. 3

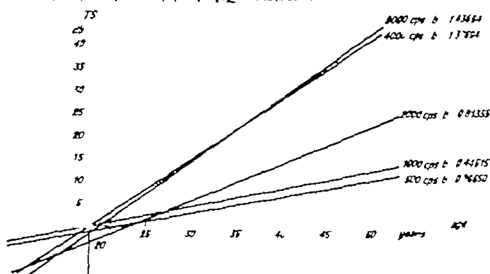


Fig. 3

RESULTS

1. *The Dependence of the Threshold Shift on Age*

(*a*) As expected the threshold shift increases with age. This fact can be readily demonstrated by regression curves (Figs. 2 and 3). The frequencies of 4000 cps [and 8000 cps] are more affected than the lower frequencies.

(*b*) As mentioned by other authors, the left ear shows an auditory threshold higher than the right ear (Glorig *et al.*, 1957; Lierle & Reger, 1958; Oppliger *et al.*, 1960) (Fig. 4).

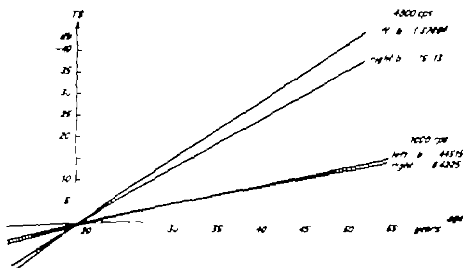


Fig. 4

TABLE 2 *Thresholds shifts (dB) at 40 years of age*

	cps	500	1000	2000	4000	8000
Present study (flying staff)	Rt. ear	1.50	8.29	11.20	23.82	21.62
	Lt. ear	1.67	8.37	12.87	28.49	28.37
Other authors						
de la Ros (1953)		~7	~7	~9	~13	~14
Glorig et al. (1954), Wisconsin State Fair						
	Rt. ear	1.0	4.1	5.1	18.8	
	Lt. ear	1.6	4.6	6.2	21.5	
Amer. Stand. Ass. (1954)					~12	
Carno (1959)					~17	
Glorig (1961)			~2	~2	~12	
Hinchcliffe (1959)		1.7	1.7	2.5	5.3	3
AE (aging effect) Nixon & Glorig				1.38	7 [illegible]	

(c) Threshold shifts in the present study can be compared with the result of other authors. It is evident that in the present study there is a more remarkable threshold shift, especially in higher frequencies, than in other more or less selected groups (Table 2). This may be the consequence of other traumatizing agents, e.g. blast trauma exposure to industrial noise etc.

2. The Relation of Threshold Shift to Flying Time

This correlation, too, can be demonstrated by regression curves. From these data the following conclusions can be drawn

(a) Aging and other eventual uncontrolled damaging factors have a greater influence on threshold shift than exposure to aircraft noise during flying time

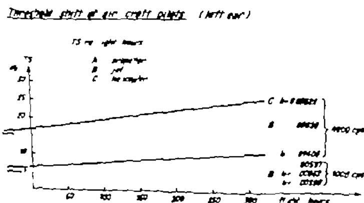


FIG. 5.

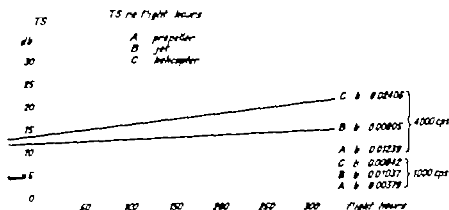


Fig 6

(*b*) The effect of the noise of helicopters on hearing is more important than that of propeller craft and jets. There is only a slight difference between the latter two, the jets being less traumatizing (Figs 5 and 6)

(*c*) The helmet worn in jets seems to be a valuable protector against traumatizing noise

Table 3 *Mult regression*

N = 5780

cps	Threshold shift dB/year ($p < 0.001$)	At 31 701 years (mean) 789 041 hr propeller 229,300 h jet 14,221 hr helicopter
500		
Rt	−0.481	−2 423
Lt	−0 [illegible]62	−2 462
1000		
Rt	−0.4408	−1 793
Lt	−0.4734	−1 682
2000		
Rt	0.5932	3 192
Lt	0. 032	0.121
4000		
Rt	−0 9451	−14 221
Lt	−1 2470	−17 060
8000		
Rt	1 1831	−13 021
Lt.	−1 4620	−16 460

3. *Multiple Regression Analysis*

The evolution of threshold shift in the present study can be determined by a multiple regression analysis, which considers both aging and noise effect simultaneously. This three-dimensional function cannot be demonstrated by two-dimensional curves. For this reason the result of this analysis is shown in the following table which demonstrates the progression of threshold shift in the study group. The mean value for the whole group shows the rate of progression per year and the hearing loss for a calculated mean age and a calculated mean flying time (Table 3).

CONCLUSIONS

Statistical evaluations of quantitative medical tests, e.g. the threshold shift in audiometry, unquestionably face limitations. Well known facts may be confirmed and new hypotheses may be generated. Simple and multiple regression analysis make it possible to study over a long period the effect of certain damaging factors on permanent threshold shift.

Presbycusis is a clearly defined process with unquestionable audiological properties (Glorig & Davis, 1961). These are known to be very complex. On the other hand, many people undergo the influence of civil, military and occupational noise, which acts as a subliminary potential or effective damaging agent. Its consequence, the so-called "sociocusis" (Glorig & Nixon, 1960) is a threshold shift practically inseparable from the aging process. By considering all the measurable factors which may influence hearing capacity it is possible to determine their real damaging effect. Individuals who fall outside the standard deviation of threshold shift might sooner or later be handicapped by a severe hearing loss. They can be examined by individual tests and eventually extricated from their damaging environment before permanent hearing loss is established.

RESUME

Nou on analyse statistiquement 786 udi grammes chez 673 a lateurs militaires ses pa la method dite de *régression multiple*. Ain i les relations entre le seu l od tif et l âge des pilotes d un part et le temp d positi n au bruit d l d autre part ont été dén ntrés. Sur la base d l ecart-type des valeurs de gression, les pilotes tteints d'u e d minuti d l'ouïe peuvent être détectés et soum a examen médical ppropcié.

ZUSAMMENFASSUNG

Die vorl egende Arbeit st t t sich auf insgesamt 3786 Schwellenau liogramm 673 Schweizer M litärpiloten. Mit einfachen und multiplen Regressionsana-

lysen wird die Progredienz der Hörschwellenverschiebungen im Verlauf der Zeit statistisch untersucht Es zeigt sich eine eindeutige Altersabhängigkeit der Regressionskurven Daneben lässt sich aber auch eine Gehörsschädigung in Abhängigkeit von der Dauer der Belastung mit Fluglärm nachweisen In Übereinstimmung mit den durchgeführten Analysen ist der Fluglärm der Kolbenmaschinen schädlicher als derjenige der Düsenjäger Aufgrund der berechneten Streuung der Regressionswerte können vorzeitig geschädigte Piloten erfasst und einer individualmedizinischen Untersuchung zugeführt werden

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Dr C von Sch lth Kla werg 31
Zu ich Sw t e land

DISCUSSION

M Portmann Tous les auteurs remarquent une différence de traumati me entre le côté droit et le côté gauche

Est-ce le fait des conditions de pilotage?

Est-ce une sensibilite plus grande du côté gauche?

Je pense plutôt à cett deu lème hypothèse Dan le cas du Mr v Schulthess, a-t il étudié statistiquem nt le trauma sonore en relation avec la latéralisation (gauchere et droitière)?

H Davis The pportunity for careful longitudinal studies of this sort is rare and should be xploited fully How long does each man remain in the study? Do the indi idual r mai i the same relation (percentage) to th group from test to test What is the base for th "threshold shift ? I it the man first audiogram or i it really the "hearing level i.e. th iso audiometric threshold?

It i good to bserve that the threshold shifts are not very large I would not expect ny of these subject to complain of impaired hearing. Did they complain?

G Shambaugh We have obtained polytome studies of th cochlear capsule in cases of presbycusis with greater-than-expected loss for the age group A ertain umber of these prove to have cochlear otosclerosis, rather than presby cusis, causing their histone loss. Th racial incidence in presb cusis noted by Rosen and mentioned by von Schulthess, wh re the African Maba n t ibe ha les presbycusis than we usually see might be due to the relative rarity of otosclerosis n negroes.

I wa impressed by the greater loss in the left ear noted by von Schulthess. Could this be due t th target practice required of Swiss military pilots, where the left ear of right-handed person suffers more n ise damage?

A Pialoux J'a remarqué de façon constante, l'anomalie signalée par M. v Schulthess hez les pilotes d Air France J ne pense pas, ain i que l a suggéré le Dr Portmann, que la cause d cett anomalie du type droitier ou gaucher mais plus implement un problèm purement physique de situation mêm du pilote placé sur la gau h d l' ppareil et d ce fait présentant un trauma plus marqué d côté gauch

v Schulthess (Reply) t M *Portmann* We do not know the reason for the differences in the threshold shift at 4000 c/s between the right nd th left ear They annot be the conseque ce of noise-influence as Glorig in hi Wisconsin Stat Fair surv y 19 7 tested an nselected group of the population and got the same results. There may be a correlation with right and left-handedness, which has ot been proved yet.

to M *Davis* The single subject i in luded in th study fo different period of time whi h depend n the age when it enters mil tary service Accordingly the ndividual exposure period t the *different kinds* of aircr ft noise varies. These fact make t ecessary t approa h the problem by the proposed statistical method

Our "threshold shift refers to the audiomet ic zero level which was ha ged according t internati nal convent on *during the period of the study* This fact is taken t consideration as ment ned in Slid 1 We agree with the discusser that the heari g loss du t flight noise i not ery pronounced in our graph. However w wish t emphasize the fact that in th curves of Figs. 7 and 8 we re dealing with mean values. There are *single* subject whose threshold-shift d ia t i f ll out of the standard deviation and we think that clinical exa mination of these may bring us loser to the problem of sen itivity to hearing-damage

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TONE PITCH INTELLIGIBILITY HEARING ADAPTATION AND FATIGUE

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Ten of 70 tested musicians and members of choirs were able to discriminate without error and remember different tone pitch and loudness thresholds. Perstimulatory fatigue for the tones C_3, C_4, C_5 and C_6 at intensities of 50–80 dB was evident Its degree was determined by the loudness balance of 35 dB in approx 2–3 min Adaptation took place during 5–10 sec depending on the sensitivity of the tested person

The ability to keep in mind correctly and precisely the loudness thresholds of different high and tone pitch perceptions does not coincide with a gifted memory for melodies and rhythms The first mentioned musical ability is called absolute tone pitch intelligibility" and is a faculty of a small number of musicians who can easily remember melodies, their rhythmical sequences, musical intervals and, of course the frequency and tonality of their different components. A musical talent means, therefore a special capacity in the rapid association of tones and melodies, which leaves in the memory more or less precise "acoustical images

The investigations of G Hensen, in year 1878 proved that the ear is very sensitive to tones of 1000 cps C_5, the difference in vibrations of this optimum audibile" amounts to 0 4–1/sec while in tones over 3000 cps (C_6, A_6 and G_7) a difference of 100 vibrations can be seen In two simultaneous resounding tuning forks the smallest interval which can be detected by the ear is to be found between 500–501 vibrations/sec which is equal to 1/60th of a half tone The ability to discriminate fractions of different tones and musical accords using various instruments was called by Jentsch the absolute connoisseurship of tones It must be stated that this kind of tone intelligibility does not make indispensable any musical ability in which there is adequate skill in the discrimination of the frequency and tonality of sounds and voices beside their rhythmical perseverance and, additionally a special capacity in the memory for melodies. As for the latter ability a great deal of observation has proved that it is easier to fix in the memory the sequences of tones than their pitch level

I had an opportunity to perform audiometrical examinations in 70 musicians, i e 8 pianists, 4 violinists, 1 composer 24 advanced students of music and 34 members of choirs (aged 21–40 years) These examinations proved that only 10 i e 4 of this group were able to remember the supraliminal loudness of the audiometric tones (Amplivox) In this test the

scale used was from C_{128} to C_{4096} cps with an intensity of 35–60 dB. At intervals of 8–15 min the same scale was repeated and the examinee asked if the intensity of the given tone corresponded with that of the loudness threshold. After an interval of 15 min this scale was used in the reverse direction, i.e. from C_{4096} cps and 100 dB to C_{32} cps and 25 dB intensity. It must be said that on both occasions the examinees, 3 pianists (aged 27, 31 and 40 years), 4 violinists (30, 32, 34 and 38) and 3 qualified students of a musical academy (21, 23 and 24) were able to discriminate precisely and remember the different tone pitch and loudness thresholds, while the other group of 60 students defined the various tones of scale too high, at an intensity of 25 dB, and then too low when tested in the reverse direction of the scale.

The errors in the loudness discrimination fluctuate on average between 10–20 dB. The 10 students with the gift of absolute connoisseurship of tones were able to discriminate and remember the different tone pitch. With regard to this question, it must be mentioned that in order to get the peratimulatory fatigue produced by a stimulus with tones of C_{1024}, C_{2048}, C_{4096} and C_{8192} I strengthened successively its intensity from 50 to 110 dB for one min. The time of recovery and restoration to normal conditions, *following fatigue* was marked by an increase in a number of decibels for every *10* sec after cessation of the fatiguing tone. The individual deviation *of* behaviour at the critical point of the stimulus intensity must be considered. In a great number of the cases examined, of 21, 27, 23, 24 and 31 years, this point was calculated to be between 90 and 100 dB and only in 3 violinists of 32, 34 and 38 did it appear just at the intensity of 80 dB.

In the first series of examined cases the magnitude of the fatigue was of a lesser degree below 90 dB. In the second series it was just below 80 dB. On the other hand, above these critical points the peratimulatory fatigue appeared at once with considerable intensity. This kind of aural fatigue must be differentiated from deafness caused by strong acoustic stimulus (stimulation deafness) as a pathological symptom, due to irritation of the cochlea by over intense tones, which is quite different from physiological fatigu[e], the critical point *of* which is bel[o]w the threshold of pain, with a tone int[e]nsit[y] *of 130* dB. It happens, *however*, that *this unusual symptom* reveal[s] itself [o]n[ly] after few to *20* min, despite the discontinuance of the above mentioned *irritation* or it persists for a shorter or longer time as a post traumatic sequele of th[is] hearing disorder (a disturbed chemical composition and bioelectrical processes within the peri-end lymph, the basilar and tectorial membranes (v. Békésy 1960, Kylin 1960).

The diagrammatic curves of the tested peratimulatory fatigue in the 10 students with absolute *connoisseurship* of tones sh[o]ws that 3 of them were m[ore] sensitiv[e] t[o] aural fatigue than the other 7, however, a logarithmic relation between th[e] time *of duration* of the short acoustic stimulus and aural fatigue was in[va]riable. In Di[a]gram (Figs. 1 and 2), in contradistinction to the high tones of C_{1024} [illegible] cps, the lower tones produce a limited

variety of fatigue which is not constant with the stimulus intensity of the testing tone this particularly justifies the concept of a dual mechanism of acoustical sensations, i e the high tones are perceived by that part of the cochlea which is exposed to the static variations of pressure and the middle-low tones which accomplishes because of the varying phasic changes in the *endolymph towards helicotrema as well*

Perstimulatory fatigue in the 10 students during the masking of the contralateral ear did not depend on the stimulus intensity but rather on the response of the nerve elements of the inner ear (Stevens & Davis, 1938 Hood 1955) Using an appropriate arrangement to stimulate both ears by tones of the same frequency i e 500–1000 cps and 80 dB intensity varying at the tested ear only (but the opposite ear was under the influence of the loudness of the constant tone) The type and degree of auditory fatigue was determined by the intensity of the variable tones (loudness balance) which in the tested cases reached their maximum of 35 dB in about 3 min remaining at an invariable level

It is notable that in contradistinction to poststimulatory fatigue perstimulatory fatigue resembles the recruitment phenomenon The state of recovery of *perstimulatory fatigue takes place quickly* during the first 5–10 sec, then decreases slowly until its maximum is reached in 50–60 sec. This particularly justifies the assumption of Matthews that in such cases there exists a regeneration of the neural elements within the peripheral part of the auditory apparatus Even the relation of the above mentioned process to the intensity of the auditory stimuli indicates that the perstimulatory fatigue increases with the stimulus intensity while individual sensitivity to the *fatiguing* tone or other conditional psychical *factors must* be taken into consideration

Working from the investigations of Ruben & Sekula (1961) Brunetti (1961) and Palva (1954) I was able to show that the perstimulatory fatigue in the tested cases was considerably shortened by using simultaneously the visual olfactory gustatory or thermal (skin) stimuli, which in turn indicates the dependance of the fatigue in question on the central nervous system in particular the reticular formation (Maspetiol *et al* 1961) As for the post stimulatory fatigue there is a remarkable increase when the stimulus intensity crosses a certain point of the critical level It is interesting that in all 10 students endowed with absolute tone pitch intelligibility perstimulatory fatigue appeared steady after 2–3 min at the intensity of 80–90 dB confirming its dependence on the magnitude of the receptor area within the cochlea in particular on the number of external and internal hair cells following fatigue This kind of aural fatigue passes our comprehension on the physiological activity of the inner ear and reticular formation receptors and now it must be considered from the point of view of the law governing *neural activity (Stevens & Davis 1938)*

Alternate balance using stimuli of constant intensity and duration from 1–5 min to the tested ear then a tone of the same frequency and varying



Fig. 1

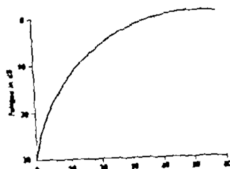


Fig. 2.

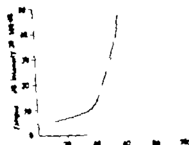


Fig. 3.

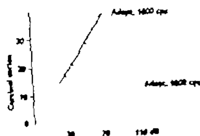


Fig. 4.

Fig. 4 A comparison bet een the slow cortical potential mov1 g from th dlecn-cephalogram and the cochlearencephalogram.

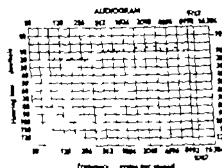


Fig. 5.

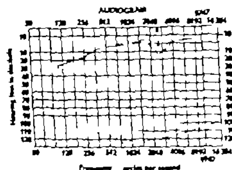


Fig. 6.

intensity t the contralateral ear supplied the peratimulatory fatigue of the 18 student with such particular that the fatigued ear during acoustical stimulation persisted for a time despite cessation of the fatiguing tone of C_{1000} cps. E en when this acoustic stimulus was applied again after a lapse f 10–60 sec and its previous sudden interruption, an unfatigued level appeared at first foll wed by rapid relapse to the fatigue level, which could be seen clearly in these tested cases. The state of recovery appeared most



F 7

clearly during the first ten seconds, reaching its peak point after 60 sec similar to the recovery process of adaptation (Diagram (Fig 3)) Hearing adaptation and perstimulatory aural fatigue have quite different meanings, the former indicating one physiological process of recovery from the disturbed condition of the latter (M Portmann & Cl Portmann, 1954 Lüscher 1952 Hahn 1962 Szpunar 1953) Experiments on animals revealed that it could be stated that the short adaptation of the Corti organ, contrary to the longer one taken from the auditory cortex It means the difference between the peripheral and central adaptation It could also be proved that one restraining influence on the adaptation phenomenon within the Corti organ from the auditory cortex and the central auditory pathways as well as through the efferent fibres The adaptation test in normal and inner ear disturbances, using the computer technical mediator revealed one characteristic difference between the slow acoustical cortical potentials, getting from the audioencephalogram and the cochlear one (Fig 4)

In order to complete the total audiological examination and physiological factors involved in tone and loudness perception by these musicians endowed with absolute tone pitch intelligibility I used additionally three hearing tests Jerger's "Sisi Feldmann's and Fowler's tests. The *first* is a simplified method to delineate the difference in tone intensity by stimulation of the ear with lower tones and simultaneously a constant loudness of equal intensity of 20–40 dB in the opposite ear The tested person perceives the tones 250–8000 cps at an intensity of 20 dB during two min at which point this intensity is augmented every 5 sec with 1 dB i e we can note 20

elevations in the audiogram during two min as an equivalent of 100% of the normal "Sisi" test (Fig. 5)

In the modified dichotic Feldmann's test the threshold curve and loudness control equality is denoted at first, then a 3000 cps tone of 80 dB is included for 4 min while the threshold point of the loudness is established. Performing the last survey one min after switching off the loudness control we get an adaptogram in which the *a* squared area indicates the efficiency of the organ of Corti and the *b* area the efficiency of the ganglion or cochlear nerve. It must be mentioned that the normal values for the *a* area are calculated to 300–500 and that of the *b* area to 1000–1500 mm²

Fowler's test, modified by Lüscher-Zwislocki, was performed too. Using certain modifications of the first two tests on the whole margin of its scale and intensity of 20–30 dB I achieved in the 24 advanced students of music auditory threshold tracings which become narrower i.e. from 12–0.3 dB, not only during the increase in intensity but also in frequency up from 1250 cps. The normal threshold for intensities 15–20 dB was calculated as 1.5–4 dB and for 50 dB as 1–3 dB

Having performed Fowler's modified test, I was convinced that the threshold values are higher than those obtained by the authors of the original test in question (Fig. 6). The threshold differentiation of loudness by the 10 students endowed with absolute tone pitch intelligibility was generally lower corresponding more or less to the details given by Knudsen & Jones, 1931, Shenshore 1890 and Tieplow quoted by Sielurycki, 1966. Even the ability to keep in mind the loudness thresholds of different high tone and supraliminal pitch perceptions showed a certain deviation with a tendency to drop downwards. Regarding the bone conduction test in the 10 student I stated that the crossperception of the tones C_1 and C_2 was evident at a weak intensity of 4–7 dB when the receptor was placed on the parietal region of the head but it was much clearer especially at lower frequencies, and at the same intensity when Jendrassik's manoeuver Ty II was applied, i.e. a strong compression of the examiner's hand by the examinee (Fig. 7). This manoeuver consists in the mobilisation of the α and fibres a th component of the motor nerves, while the receptors of Golgi Mazzoni-like type nerv endings lying around the muscle fibres and their tendinous lengthenings of the skeletal muscles, including tensor tympani and tapedius, are set in action

RESUME

La perceptio des gus, l'adaptat on et la f tigu sont examinées hez 70 mus en 10 ont pu discerner et se rappeler san ucune erreur les differentes hauteurs des son et les seuils d audition, la f tigue pour les son C 3, C 4, C 5, C 6, pour l'inten ité de 50–80 dB etait évident L daptation se f isait pendant 3–10 sec Il dependait d la sen ibil té l di idnell La f tigu a été mes ré par l'epreuve de Fowler (35 dB en 2–3 m n)



FIG 7

clearly during the first ten seconds reaching its peak point after 00 sec, similar to the recovery process of adaptation (Diagram (Fig 3)) Hearing adaptation and perstimulatory aural fatigue have quite different meanings, the former indicating one physiological process of recovery from the disturbed condition of the latter (M Portmann & Cl Portmann, 19o4 Lüscher 1952 Hahn 1962 Szpunar 19o3) Experiments on animals revealed that it could be stated that the short adaptation of the Corti organ, contrary to the longer one taken from the auditory cortex It means the difference between the peripheral and central adaptation It could also be proved that one restraining influence on the adaptation phenomenon within the Corti organ from the auditory cortex and the central auditory pathways as well as through the efferent fibres The adaptation test in normal and inner ear disturbances, using the computer technical mediator revealed one characteristic difference between the slow acoustical cortical potentials, getting from the audioencephalogram and the cochlear one (Fig 4)

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ZUSAMMENFASSUNG

Zehn von 70 untersuchten Musikern und Mitgliedern von Gesangvereinen waren im Stande verschiedenartige hohe Grundtöne und lärmartige Schwellen fehlerfrei zu unterscheiden und sich an sie zu erinnern Hörermüdung für die Töne C_3, C_4 C_5 C_6 in der Stärke von 50–80 dB war deutlich deren Grad durch Lärmtonschwellen Ausgleich von 35 dB in ungefähr 2–3 Min bestimmt wurde Adaptation fand während 5–10 sec statt und zwar abhängig von der Empfindlichkeit des Untersuchten

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ÉTUDE D'UNE MÉTHODE D'EXPLORATIONS FONCTIONNELLES DES SYNDROMES VESTIBULAIRES PAR L'ASSOCIATION DE L'ÉLECTRONYSTAGMOGRAPHIE, DE L'ÉLECTROMYOGRAPHIE ET DE LA STATOKINÉSIMÉTRIE

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Notre travail a été entrepris dans le but d'adapter un nouvel appareil d'enregistrement, le statokinésimètre, aux explorations fonctionnelles otoneurologiques. Cette étude a été réalisée sur 71 sujets normaux et pathologiques et nous a finalement permis de préciser les grandes lignes d'une méthode dont le principe est d'associer trois techniques d'enregistrement pour connaître d'une façon plus détaillée la réponse à une stimulation vestibulaire calorique.

TECHNIQUES D'ENREGISTREMENT

Statokinésimètre

Cet appareil permet d'étudier les déplacements, dans les quatre directions cardinales, du centre de gravité d'un sujet en station verticale.

L'appareil comprend: une bascule comportant un système de capteurs de pression sur lequel se place le sujet en position de recherche du signe de Romberg; un système d'enregistrement traduisant les variations de pression dues aux déviations captées par la bascule.

Pour les épreuves que nous avons réalisées, l'appareil original a été modifié de telle sorte que l'enregistrement des déplacements du centre de gravité soit fait en fonction du temps sur un inscripteur à plume Visiograph Alvar, deux lignes étant réservées: l'une aux déviations antéro-postérieures, l'autre aux déviations latérales.

Electronystagmographie

Des électrodes d'argent chloruré sont mises en place selon la façon habituelle pour l'étude des déviations horizontale et verticale. L'enregistrement est fait sur deux des quatre voies EEG du Visiograph.

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Au total on dispose de 6 lignes d'enregistrement Electromyographie postérieure et antérieure électronystagmographie horizontale et verticale déviations antéro-postérieure et latérale

PROTOCOLE D'EXAMEN

Après les réglages et calibrations des 6 voies d'enregistrement, le sujet est prié de monter sur la bascule où il se tient debout, les pieds nus, dans la position du garde à vous. Plusieurs épreuves sont alors faites

– On étudie les déplacements volontaires du sujet dans les 4 directions et l'activité électromyographique concommittante

– un enregistrement est ensuite fait en demandant au sujet de regarder dans l'obscurité une barre verticale phosphorescente placée à 3 mètres devant lui pendant 30 secondes

puis on effectue un enregistrement de même durée et dans la même position, mais les yeux fermés.

Ces épreuves préliminaires étant terminées, (et après avoir constaté que le sujet était normal) sa tête est inclinée d'environ 60 en arrière les yeux étant fermés. Après que l'on ait noté la position du centre de gravité sur l'enregistreur un *réglage est effectué* pour placer les plumes en position médiane

STIMULATION

La stimulation de l'appareil vestibulaire est faite après vérification du conduit auditif externe par irrigation calorique à la seringue avec de l'eau à 21 Plusieurs doses sont utilisées pour chaque oreille 2 cc et 4 cc, avec un débit de 1 cc *par seconde* Après les irrigations, l'enregistrement est poursuivi pendant 1'30 à 2'30 suivant l'intensité de la réponse Ensuite le sujet se repose en position assise Un contrôle de la disparition du nystagmus dans la position de stimulation est effectué avant chaque nouvelle irrigation.

RÉSULTATS

Déviations

Les déviations se font toujours en avant et du côté de l'oreille irriguée

— Les déviations latérales sont les plus précoces, elles apparaissent au bout d'un temps moyen de (2 cc) 9 sec (4 cc) 7 sec

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Au total on dispose de 6 lignes d'enregistrement : électromyographie postérieure et antérieure, électronystagmographie horizontale et verticale, déviations antéro-postérieure et latérale.

PROTOCOLE D'EXAMEN

Après les réglages et calibrations des 6 voies d'enregistrement, le sujet est prié de monter sur la bascule où il se tient debout, les pieds nus, dans la position du garde à vous. Plusieurs épreuves sont alors faites :

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Ces épreuves préliminaires étant terminées, (et après avoir constaté que le sujet était normal) sa tête est inclinée d'environ 60° en arrière, les yeux étant fermés. Après que l'on ait noté la position du centre de gravité sur l'enregistreur un réglage est effectué pour placer les plumes en position médiane.

STIMULATION

La stimulation de l'appareil vestibulaire est faite après vérification du conduit auditif externe par irrigation calorique à la seringue, avec de l'eau à 24°. Plusieurs doses sont utilisées pour chaque oreille : 2 cc et 4 cc, avec un débit de 1 cc par seconde. Après les *irrigations*, l'enregistrement est poursuivi pendant 1'30" à 2'30" suivant l'intensité de la réponse. Ensuite le sujet se repose en position assise. *Un contrôle de la disparition du nystagmus dans la position de stimulation est effectué avant chaque nouvelle irrigation.*

RESULTATS

Déviations

Les déviations se font *toujours* en avant et du côté de l'oreille irriguée.

Les déviations latérales sont les plus précoces, elles apparaissent au bout d'un temps moyen de (2 cc) 9 sec. (4 cc) 7 sec.

— La déviation antérieure lui succède elle apparait en moyenne au bout de (2 cc) 11 sec, (4 cc) 10 sec.

Leur durée est au minimum de

— latérale (2 cc) 55 sec, (4 cc) 91 sec

— antérieure (2 cc) 66 sec, (4 cc) 115 sec

En réalité les déviations se prolongent le plus souvent au-delà de la fin de l enregistrement

Il semble néanmoins que les déviations latérales soient légèrement plus courtes que les déviations antérieures

Electromyographie

a) *Au repos le triceps sural est en activité permanente. Cette activité* parait être en relation avec la déviation postériure du centre de gravité rencontrée normalement chez tous les sujets.

— Par contre le jambier antérieur est dans la plupart des cas silencieux

b) Lorsque l on demande au sujet de se déplacer volontairement dans le sens antéro-postérieur on constate que

— le déplacement du centre de gravité en avant s accompagne d une importante activité isolée du triceps sural,

— alors que le déplacement en arrière s accompagne d une importante activité isolée du jambier antérieur

Ces activités suggèrent qu au cours des déplacements du centre de gravité et pourvu que la plante des pieds reste en contact avec la bascule, ces deux muscles s opposent à des mouvements de grande amplitude

c) Après la stimulation calorique on constate des résultats variables

— soit une absence de modification de l activité de repos,

— soit un renforcement isolé de l activité du triceps sural qui apparait en moyenne après (2 cc) 17 sec, (4 cc) 13 sec lorsque le déplacement antérieur attent sa valeur maximum et persiste jusqu a ce que le sujet ait tendance à revenir à la position d équilibre normal

Chez certains sujets le jambier antérieur est le siège d une activité modérée apparaissant après (2 cc) 20 sec, (4 cc) 9 sec, donc approximativement contemporaine de l activité du muscle postérieur et de la déviation antérieure maximum

Dans certains cas cependant cette activité est très précoce et parait due à des oscillations vers l arrière que l on constate parfois au début des réponses

Il est apparu d ailleurs que l activité du jambier antérieur dure moins longtemps que la déviation du centre de gravité

De ces enregistrements il ressort que l activité de ces muscles a en général un rôle de frein contrôlant les déplacements du centre de gravité qui compromettent l équilibre lors des stimulations vestibulaires Néanmoins, l activité de base du triceps sural dans la position de repos évoque davantage une *action* de poussée vers l avant s opposant à une chute en arrière

Il nous est encore difficile actuellement de distinguer avec précision les caractéristiques de fonctionnement de ces muscles dans les conditions d'examen et d'enregistrement que nous utilisons.

De toute façon, alors que les déviations sont maximum, on assiste en général à une très intense activité électromyographique qui disparaît lorsque le sujet tend à revenir à sa position d'origine.

Electronystagmographie

De très nettes réponses horizontales, battant du côté opposé à l'irrigation apparaissent après un temps de latence de (2 cc) 22 sec. (4 cc) 25 sec correspondant aux temps classiquement décrits.

Elles durent en moyenne (2 cc) 63 sec (4 cc) 7 sec et donc se terminent en général avant le retour du centre de gravité à sa position initiale.

REMARQUES

Parmi les faits les plus saillants, il faut remarquer

1 L'apparition très précoce des déviations latérales du centre de gravité qui précèdent de plus de 10 secondes les premières secousses de la réponse électronystagmographique horizontale et se prolongent en général après la fin du nystagmus.

2 Les modifications de l'activité musculaire qui, lorsqu'elles existent, apparaissent également très précocement et semblent contemporaines des déviations statiques.

Le maximum d'activité coïncide avec le maximum de déplacement et aussi avec le maximum de la réponse E.N.G.

On constate donc

1 une dissociation temporelle entre d'une part les déviations maxima du centre de gravité et les réponses musculaires associées, et d'autre part, les réponses E.N.G. horizontales

2 une plus grande précocité des déviations latérales par rapport aux déviations antérieures

3 un seuil des déviations du centre de gravité plus bas que celui du nystagmus en effet certains sujets qui n'ont pas montré de réponses nystagmiques nettes ont cependant accusé d'importantes déviations antérieures et latérales.

Quant à la déviation en avant elle suggère que l'on stimule aussi les canaux semi circulaires verticaux.

Néanmoins, nous n'avons pas pu mettre en évidence de nettes réponses électronystagmographiques verticales

DIFFICULTES ET LIMITES DE L'EXAMEN

Parmi celles-ci citons

— sujet (âgé) ne pouvant incliner la tête en arrière,

instabilité des sujets non habitués à la station debout pieds nus,

— redressement progressif de la tête au cours de l'examen,

— mouvements de paupières accentués par le maintien forcé de la tête en arrière le sujet étant debout les yeux fermés

— variabilité individuelle de l'activité musculaire dans le maintien d'une position d'équilibre

Il est en outre vraisemblable que l'effort réalisé pour maintenir la tête dans la position d'examen entraîne une déviation vers le bas de l'œil qui bloque le nystagmus vertical

Sur le plan matériel il faut noter

— les difficultés de réglage

— l'absence de mesure quantitative des déviations,

— la nécessité 1 d'enregistrer l'électromyogramme des deux jambes, car l'activité est plus grande du côté de l'irrigation et il est possible en particulier chez certains sujets que les muscles de la jambe droite aient une activité prépondérante 2° de faire l'irrigation calorique avec le plus de précision possible

Intérêt

L'association de ces 3 techniques complémentaires permet

— d'effectuer une étude objective et séparée des déviations antérieure et latérale dont on remarque la grande sensibilité et la précocité par rapport à la réponse électronystagmographique

— de préciser la physiologie des muscles de la jambe et leur rôle dans l'équilibration

SUMMARY

This study is designed to show the static modifications in patients having equilibrium troubles.

The tests are performed with or without vestibular stimulation with the aid of

1 A statokinesimeter with which can be recorded
The position of the center of gravity compared to the polygon of support.
Its shifting in the four cardinal directions

2 An electromyograph which records simultaneously the electrical activity of some muscular groups.

3 An electronystagmograph

ZUSAMMENFASSUNG

In der vorliegenden Arbeit wurde eine neue Aufzeichnungsapparatur für oto-neurologische funktionell Untersuchungen das Statokinesimeter auf ihre praktische Anwendbarkeit hin ausprobiert Die Untersuchungen wurden an 71 normalen und pathologischen Versuchspersonen durchgeführt Aus den gewonnenen Erfahrungen resultierte schliesslich eine Untersuchungsmethode die im wesent

lichen auf den Aufz lehnungen von 3 verschiedenen Einzelmomenten basiert und in detaillierter Form die Reaktion auf kalorische Vestibularstimulationen erk n-nen lässt.

Clinique ORL d la Faculté d Médecine d Paris
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DISCUSSION

A. M Morgon I ha been much interested in your beautiful communication. Functional exploration of vestibular nystagmus is not always easy. This method might give more reliable results in syndromes with peripheral and central elements, or poorly understood disri ess, than with classic procedures of vestibular investigation.

I would lik to ask whether recording of the ctivity of the neck muscles wa part of th ir investigation

M Arslan The findings of Mr Pialoux *et al.* demonstrate clearly that every estibular ex itation provokes a functioo l variation by all th muscles of the body as the vestibular ystem is strictly connected with the extrapyramidal yst m this fact means that th estibula activity is continuously hecking the muscular function.

N Torok I want t congratulate the uthors on the ingenioo multiple approach for asses ing vestibular sensiti ity Nystagmu alone may ot be the best measure t least i certai instances, *in the evaluation of the pathological estibular stat* Nystagmic nd estibulo-spinal *responses are not identical.* I our experience heteropulsion is longer lasting response than nystagmus. One question I would l ke to sk Is it not difficult to ha a *patient with dizziness or equilibratory* disorders to tand while nystagmus recording i carried ut? This procedure requires full rela ation O the *other hand, the* often apprehensi e dizzy patient' muscle t at nd st ll enough t Perform Romberg test.

L. B B. Jongkees J félicite M Pialou et ses collaborateurs d leurs résultats vec la stat kinésimétri Je me demande si le f it que le déplacement du centre de gravité se montre vant le nystagm et disparait après lui n est pas causé parce qu l ont enregi tré la phase rapide En enregistrant la phase lent du stagmu il n uraient probablement pas trouvé ces différences.

P P aloux (Répo se) À M. *Morgon* Nou n a on pas encore fait d enregistrement des muscles de la nuque Nous espérons que cett technique nous permettra d etud er er plus de préc sion les ca d di sociation clinique e tre les sensat ons de erti ge et l'absence ou la presence de yst gmus.

M A slan De n mbreu m scles sont en ffet mi en activité par une stimulation vestibula re et jouent un rôle important dans l'équilibre Nou espé ron pour en preciser le rôl grâce à c tte méthod d enregistrement.

M. Torok Il est certain que le nystagmus n'est pa le seul sign intéressant à étud er et nou penson qu'il aura beaucoup à pprendre de l'association d ces 3 regi trements. Quant au d fficultés lles sont certes nombreuses. En particulie l est raisemblable que certain sujets pathologiques seront très difficiles am er De tout façon ette méthode nous apport des inf rmation intéres-sa tes sur le pla de la phy iologie normale

M J ngkees La phase lente est certainement d'un importance capitale dan l' t de lu n st gmus. Les condition particulières de ces enregistrements rendent

— redressement progressif de la tête *au cours de l'examen*
— mouvements de paupières accentués par le maintien forcé de la tête en arrière le sujet étant debout les yeux fermés.
— variabilité individuelle de l'activité musculaire dans le maintien d'une position d'équilibre
Il est en outre vraisemblable que l'effort réalisé pour maintenir la tête dans la position d'examen entraîne une déviation vers le bas de l'œil qui *bloque le nystagmus vertical*
Sur le plan matériel il faut noter
— les difficultés de réglage,
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L. B. W. Jongkees J félicit M. Pialoux et ses collaborateurs de leurs résultats er la statokinésimétrie Je me demande si le f it que le déplacem nt du centre de gravité se montre ant le nystagmu et d sparaît après lui n est p e usé parce qu il ont enregistré la *phase rapid* En enregistrant la phase lente du stagmus il auraient probablement p s trouvé ces différences.

P. Pialoux (Répo se) à M. *Morgan* Nou n avons pas encore f it d enregistrement des muscles de la nuque ous espérons que cett technique nou permettra d étudier er plus de précisi on les cas de dissociation clinique ntre les sensa- t ns de rtige et l'absence ou la présence d nystagmus.

M. *Arslan* De nombreu muscles sont en effet mis en acti ité par une stimulation estibulaire et jouent un rôle important dan l'équilibre Nou espé- on pouvoir en préciser le rôle grâce à cett méthode d'enregistrement.

M. *Torok* Il est certain que le nystagmus n est pas le seul signe intéressant etudier et non pensons qu'il aura beaucoup à apprendre de l ssociation de 3 enregistrements. Quant ux difficultés elles sont certes nombreuses. La parti- lier l est ra semblable que certa s sujet pathologiques seront très difficiles ent er De tout façon cette méthode nous apporte des informations intéressantes sur le pla d la physiologie normale

M. *Jongkees* La phase lente est certainement d u import nce capital dans l'étude du nystagmus. Les cond tions particulières d ces enregistrements rendent

malheureusement l'étude détaillée du nystagmus difficile. De toute façon cette méthode d'examen ne peut être indiquée qu'après avoir pratiqué les épreuves vestibulaires habituelles.

The study is designed to show the static modifications in patients having equilibrium troubles. The tests are performed with or without vestibular stimulation with the aid of: (1) A statokinesimeter which allows the recording of the position of the center of gravity compared to the polygon of support, its shifting in the four cardinal directions and the quick correcting movements during a vertical stand of variable duration (generally one minute). (2) An electromyograph which records simultaneously the electrical activity of some muscular groups.

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GALVANIC TEST IN CENTRAL VESTIBULAR LESIONS

C. R. P Pfaltz, M.D and Y Koike, M.D

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1 Brainstem lesion without presence of a spontaneous vestibular nystagmus generally do not show any particular change of the pattern of the galvanic nystagmus reaction s.

2. In brainstem lesions with presence of a spontaneous nystagmus the threshold of the galvanic nystagmus is mostly normal whereas supraliminar test invariably show a pathological reversal phenomenon Sometimes a relatively high incidence of abnormally increased amplitude and frequency values can be found phenomenon which is not observed among other groups.

3 Cerebello-pontine angle tumours (acoustic neuroma excluded) show either a normal or slightly moderately raised nystagmus threshold.

4 In supratentorial lesion of the brainstem the pattern of liminar and supraliminar galvanic responses is not characteristic

In lesion of the cerebral cortex threshold values are normal among the majority of the cases but supraliminar test reveal relatively high incidence of pathological directional preponderance towards the side of the lesion which may also be combined with corresponding directional preponderance of optokinetic nystagmus.

INTRODUCTION

Galvanic stimulation of the human vestibular system causes both a disturbance of the equilibrium and nystagmus. The fast component of perstimulatory galvanic nystagmus is directed towards the side of the negative electrode whereas poststimulatory galvanic nystagmus beats toward the positive electrode According to the experimental findings of Ledoux (1958) this nystagmic response may be explained by an electric polarisation effect of both the sensory cells of the vestibular end organ and the cells of the vestibular ganglion. The catelectrotonus probably facilitates and increases the rhythmic bioelectric activity of the vestibular sensory and ganglion cells whereas the anelectrotonus seems to exert an inhibitory action upon neuronal activity

The most important feature of the galvanic test is the persistence of the galvanic reaction following *complete destruction* of the vestibular endorgan and on the other hand abolition of the nystagmic response as soon as the peripheral vestibular neuron is damaged (Dohlman 1929) Hence it may

be said that the origin of galvanic nystagmus depends entirely upon the integrity of neuronal elements of the vestibular ganglion and upon the conductivity of the nerve fibers Taking these facts into account the galvanic test is the only diagnostic procedure allowing the differentiation of an endorgan lesion from a lesion of the peripheral neuron This test is therefore of greatest diagnostic importance with respect to the detection of an acoustic neuroma at an early stage Owing to the lack of appropriate recording methods the properties of both per and poststimulatory galvanic nystagmus were not well known until recently Mainly for this reason the galvanic test has been neglected for a long time as a diagnostic procedure its results being too inaccurate to give proper information. The recording of galvanic nystagmus is made feasible only by the use of *photo-electro-nystagmography* because during galvanic stimulation nystagmography based on the derivation of corneo-retinal potentials, does not reproduce ocular movements properly but picks up a rheogram (Gaberšek & Jorbert, 1965)

In previous papers (Pfaltz & Richter 1965 Pfaltz, 1965 1967) we have tried to establish the criteria which are essential for the evaluation of a galvanic nystagmus recorded photoelectrically Under physiological conditions *perstimulatory galvanic nystagmus* shows a rather constant pattern whereas *poststimulatory galvanic nystagmus* is more variable with respect to frequency and amplitude For this reason we invariably evaluate *perstimulatory galvanic reactions* for diagnostic use

In a first series of nystagmographic studies (Pfaltz & Richter 1965 Pfaltz, 1965 1967) we have confirmed the results of Dohlman's animal experiments in normal human subjects as well as in patients suffering from vestibular disturbances of peripheral origin In the present study we intend to investigate the problem of the diagnostic value of the galvanic test in vestibular disturbances of central origin

METHODS OF RECORDING AND STIMULATION—TERMINOLOGY

The *"differential method" of photoelectric recording* of nystagmus as developed by Richter & Pfaltz (1955 1958) works on the principle that two photoelectric cells, placed so their medial edges aim at the medial and lateral junctions of the iris and cornea respectively with an interposed infra red light source on the pupil will record any change in the position of the eyeball by a relative change in the amount of reflected light received by each photoelectric cell Artefacts caused by muscle tremor and by changes of the per ocular electric field occurring frequently during galvanic stimulation are mainly eliminated by a photoelectric recording device

Bipolar-binaural galvanic stimulation is preferred to various monaural and unipolar methods of stimulation because of its more constant results (Pfaltz, 1965) The intensity of the current is controlled by a milliampère meter The following criteria are used for the evaluation of the nystagmic response evoked by both *liminar* and *supraliminar* galvanic stimulation

1 *Threshold values may vary in normal individuals from 1–2 mA*

Nystagmus intensity expressed by frequency (number of beats per time unit) and *amplitude* varies at *threshold* level between 0.2–1.8 jerks/second and 0.3 –1.9 /nystagmus beat (normal range of distribution—statistically evaluated)

2 *Reversal phenomenon*

Every sudden change in the direction of the galvanic current 4–6 mA *above threshold level* instantaneously causes an abrupt *reversal of the per stimulatory nystagmus*. Nystagmus intensity following the reversal of the current is considerably increased 1.4–2.0 beats/second and 1.5–2.0 /nystagmus jerk (normal range of distribution—statistically evaluated) The difference between the two nystagmus reactions following the *sudden change of the direction* of the galvanic current should not exceed 15% of the total reaction for both frequency and amplitude.

The value of the difference (*D*) is calculated from the following formula

$$D\% = \frac{(a+b)}{(a+b)} \times 100$$

a = *number of beat* or total amplitude of left-beating nystagmus during a sample period of 10 seconds following reversal of the current (4–6 mA above threshold)

b = the same values for right-beating nystagmus

D-values exceeding 15% indicate a *pathological directional preponderance* (statistical evaluation $\bar{x} = 8.4\%$, $sD = 3.3$)

RESULTS AND CONCLUSIONS

Out of 180 cases with disorders *of the central* nervous system we have selected 75 patients in which an accurate diagnosis had been established with respect to the localisation and the nature of the lesion either by means of a complete neurological ophthalmological and otoneurological examination or by neurosurgical intervention and finally in some cases by autopsy The 75 cases are subdivided into the *following* five groups

1 Brainstem lesion without presence of spontaneous nystagmus 20 cases.
2 Brainstem lesion with presence of spontaneous nystagmus 20 cases.
3 Pontocerebellar lesion 10 cases.
4 Subcortical lesion 10 cases.
Cortical lesion 15 cases.

1 In *lower brainstem lesions* showing a rather mild symptomatology the pattern is not very characteristic but for an occasional combination of raised threshold values *and* normal suprathreshold reactions.

In lesions involving *the pons and the midbrain* area the pattern of

be said that the origin of galvanic nystagmus depends entirely upon the integrity of neuronal elements of the vestibular ganglion and upon the conductivity of the nerve fibers. Taking these facts into account the galvanic test is the only diagnostic procedure allowing the differentiation of an endorgan lesion from a lesion of the peripheral neuron. This test is therefore of greatest diagnostic importance with respect to the detection of an acoustic neuroma at an early stage. Owing to the lack of appropriate recording methods the properties of both per- and poststimulatory galvanic nystagmus were not well known until recently. Mainly for this reason the galvanic test has been neglected for a long time as a diagnostic procedure, its results being too inaccurate to give proper information. The recording of galvanic nystagmus is made feasible only by the use of *photo-electronystagmography*, because during galvanic stimulation nystagmography based on the derivation of corneo-retinal potentials, does not reproduce ocular movements properly but picks up a rheogram (Gabersek & Jorbert, 1965).

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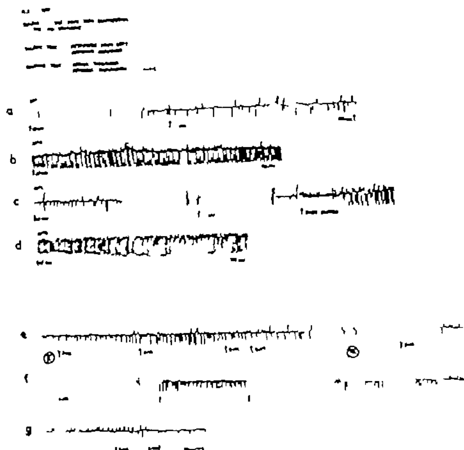


Fig. 2. *a–d*. *Cal... test*. No responses from left labyrinth. (*e–g*) *Galvanic test*. (*e*) Threshold of nystagmus to the left 1.2 mA. (*f*) Threshold of nystagmus to the right 1.2 mA. (*f*) and (*g*) Sudden reversal of current evokes both nystagmus to the left and to the right with directional preponderance to the left, i.e. to the side of the lesion.

tation of gaze (Monnier 1907) show the most constant pathological findings of this particular type (Fig. 3).

Summing up our results we may conclude:

(*a*) In cases of lesion involving the central nervous system the pattern of nystagmus following liminar and supraliminar galvanic stimulation of the vestibular system is quite different from the pattern observed in lesions of the vestibular endorgan or its peripheral neuron.

(*b*) Lesions of the cerebral cortex show a pattern of the galvanic responses which is very different from those observed in brainstem lesions. Furthermore in brainstem lesions galvanic stimulation reveals again two different types of response-patterns, depending obviously upon the localization of the functional disorder. This observation is in agreement with the

FIG. 1 (a) *Threshold test* Threshold of nystagmus towards the right 2 mA and towards the left 2 mA (b) and (c) *Supraliminar test* Reversal of current (R) at 6 mA does not elicit any nystagmus toward the left

galvanic responses shows two characteristic features we may either find complete abolition of galvanic nystagmus directed towards the side of the lesion occurring in functional disturbances of the *pons* We have been tempted to attribute this unilateral abolition of galvanic nystagmus to a lesion of the vestibular nuclei because some of these cases present also an ipsilateral nuclear facial palsy (Fig 1)

In lesions of the *midbrain* area we observe more frequently than among other groups, cases presenting increased amplitude and frequency values of galvanic nystagmus Hypothetically this particular pattern may be attributed to a lesion involving inhibitory centers located within the reticular substance at this level

3 *Cerebello-pontine-angle tumours* which do not originate primarily from the vestibular nerve such as the classical acoustic neuroma, impair blood circulation within the labyrinth long before the conductivity of the vestibular nerve is impaired or abolished by tumour pressure That may explain our observations made within this group i e deafness and abolition of caloric responses combined with normal galvanic reactions at threshold level (Fig 2)

4 *In cortical lesions galvanic responses are quite different from those* observed among other groups Nystagmus threshold is invariably normal, whereas supraliminar stimulation nearly constantly reveals a marked directional preponderance towards the side of the cortical lesion It is sometimes combined with a *corresponding directional preponderance of the opto-*kinetic nystagmus but hardly ever of the caloric responses Lesions of the occipito-temporal cortex, an area which facilitates the ipsiversive slow de-

2) Les lésions d tronc cérébral accompagnées d un nystagmu vestibulaire spontané modifient la réactio galvanique différemment suiva t leur extension t leu caractère Lorsqu lles sont étendues et mal délimitées, le seuil du nystagm gal nique reste norm l la plupart du temps, alors que les stimulation supraliminaires atraînent un ogmentation pathologique de la fréquence et de l' mplitud

3) Les tumeurs d l'angle ponto-cérébelleu n'influencent qu peu ou pas du t t le seuil du nystagmus.

4) Lors d lésions supratentorielles du tronc cérébral, la réaction gal anique rest normale dan la plupart des cas.

) Une lesion du corte cérébral ne modifi pas le seuil d nystagmus gal an q Le phé omène d'inversion se manifeste par contre lors de stimulation supral minaires sous l forme d'un prépondéranc directionnelle du ôté de la lesion Des Isolés présentent n plu une prépondéran e directionn lle du st gmus optocinétique également dans le même sens.

ZUSAMMENFASSUNG

1) Il rnst mmläsionen ohne Anwesenheit eines vestibulären Spontan ystagmus lassen m wesentlich n ine normal galv nische Reaktion erkenne

2) Hirn tammläsionen mit Anwesenheit eines vestibulären Spontannystagmus f hren zu f lgend n Veränderungen der galvanischen Nystagmus-Reaktion Schw lle meist norm l, uberschw llige Reizung path logisch (abnorm hohe Ampl tuden- und Schlagzahlwerte) In Fallen einer umschriebenen Hirnstammlä ion mit gl i hze liger ankleitr Facialisparese wird häufig ein Aufhebung sowohl des thermisch) ech des gal anisch usgelösten Nystagmus in Richtung zur Lä ion beoba htet.

3) Tumoren des Klei h rnbrü kenwinkels la sen in der Mehrzahl) Fälle entweder ine norm le oder nur in leicht erhöht Nyst gmusschwelle erken en w hrend se be m echten Akustikusneurinom f t usnahmslos pathologisch erhöht (t (> 10 mA)

4) Bei supratentoriellen Hirnst mmläsionen fällt die galvanisch Reaktion in der M hrzahl der Fälle normal aus.

) f f llen einer umsch iebenen horizont len Läsion des Zentral ers n sten werden in der Regel rm le Schw llenwerte f stgest llt, während bei überschw ll ger R izung n der Mehrzahl der Fälle ein path logisches Umkeh phän me na hgewiesen werden kan Meistens hand lt es ich um f Rich f gsuberw egen zu Se t der Läsion wobei in ezeln llen Fälle auch in gleichsi n ges Richtungsuberwiegen des optokinetischen N stagmu beobachtet len kann

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a

b

c

d

e

f

Fig 3. (*a*) and (*b*) *Cal le t t* Peak frequency f nystagmu t th l ft bove n rmal l el duri g th culmin tion period (*a*) but no oth path l gical patt rn (*c*) a d (*d*) *Optokineti ng tagmus* aboli hed t th l ft. ( ) d (*f*) *G l vani t t* N rm l re e ti n at threshold lev l ( ) a d (*f*) but boliti n f y t gmu to th l ft ft sudd n ev rsal of urrent at 6 mA

recent experimental findings of Potthoff *et al* (1967) wh experimentally investigated the responses of vestibular neurons t galvanic stimulation in the cat They reported the existence of two anat mically and functionally different populations of neurons one pred minating within the mesen cephalon and the other within the pontomedullary portion of the brain stem

Hence, may be concluded that liminar and supraliminar galvanic tests, performed under nystagmographic control may contribute valuable diag nostic informati n with respect to the localizati n of a central vestibular lesion

RÉSUMÉ

1) Les lésions bulbo-protub érancielles sans presence d un nystagmu vestibulaire spontané n influencent guere la réaction galvanique

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CHEMICAL EVALUATION OF INNER EAR FLUID AS A DIAGNOSTIC AID

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Biochemical analyses have been made of the inner-ear fluids of patients with otosclerosis, Menière's disease and acoustic neurinoma. Uncontaminated samples of perilymph removed from the vestibule of otosclerotic ears show normal values for K, Na, and protein. For Menière's disease fluid from the vestibule shows normal values for endolymph and from the scala tympani of the basal turn normal values for perilymph. For patients with acoustic neurinoma, the fluid removed from the vestibule and from the horizontal canal shows very high protein values even for those patients having normal protein values in the cerebrospinal fluid. Biochemical analysis of inner-ear fluid is a useful aid for difficult diagnostic problems.

A study of labyrinthine fluid biochemistry may eventually lead to an understanding of the relationship of inner ear fluids to normal hearing function and to certain types of sensorineural deafness. The diagnostic data obtained thus far also has been of value in differentiating Menière's disease from acoustic neurinoma.

A study of the chemistry of the inner ear of smaller mammals (cat) has revealed the following values

	Sodium (meq/L)	Potassium (meq/L)	Protein (mg %)
Perilymph	140	4	173
Endolymph	23	110	144
Serum	143	4	7500

These findings are in general agreement with those from other laboratories.

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DISCUSSION

N *Torok* Mr Pfaltz galvanic technique offers a breakthrough in an area where up to the present we had no way to differentiate between vestibular responses. When correlated with the more routine vestibular testings and valua tion the galvanic stimulation response assessed by the P.E.N G can differentiate location in the central nervous system which is what other vestibular assessments cannot offer

C R Pfalt (Reply) to Mr *Torok* The galvanic test is a complementary testing procedure which should be used together with other experimental labyrinthine tests such as thermic or rotatory stimulation However as pointed out before *it is a very important test for the differentiation of a lesion of the vestibular* endorgan from a lesion of the peripheral neuron As our observations have shown the galvanic test seems also to be rather helpful with respect to the loca lisation of a central vestibular lesion It is the different behaviour f the galvanic response at threshold level and the one above threshold (supraliminar stimulation i e reversal phenomenon) which we think s of particular nterest but this is a new field of in estigation and we need further information before we are allowed to draw definite conclusions.

	Case 1	Case 2
Sodium	146 meq/L	175 meq/L
Potassium	5 meq/L	7 meq/L
Protein	268 mg	325 mg

Thus, the fluid removed from the vestibule was endolymph and not altered perilymph.

The removal of perilymph from the horizontal canal of patients with proven acoustic neurinomas has revealed normal perilymph values for pot sium and sodium but markedly increased protein. This is consistent with the histological findings of a finely granular acidophilic staining precipitate in the perilymph of some ears with acoustic neurinoma. The mean alues for eleven proven acoustic neurinoma cases were as follows

Sodium	146 meq/L
Pota ium	13 meq/L
Prot n	19.. mg*

This elevated protein level was present in all eleven ears, five of which had n rmal protein values in the cerebrospinal fluid

Diagnostic labyrinthotomies were performed on eleven patients in whom it was not possibl to make a definite diagnosis between Menière s disease and acoustic neurinoma. In two, the fluid from the vestibule was charac t ri tic of endolymph and the patients subsequently were treated by laby rinthect my with relief of symptoms. Four had greatly elevated protein lev ls and subsequently had successful surgical rem val of acoustic neurinoma by the translabyrinthine route In five the sodium and potassium levels were normal for perilymph, however protein was slightly elevated These patient are being kept under observation

The diagnostic labyrinthotomy may be helpful when otologic and neurologic examinati n including audiometric and estibular tests, cerebrospinal fluid tudies and roentgenological examination fail to provide diagnostic differentiation for the patient with u pected Meni re s disease r acou tic neurin ma

RÉSUMÉ

Des anal ses biochim ques d extrait d l'oreille i terne ont été faites sur des lades souffra t d'otosclerose d maladie de Menière et de neurinom acou stiqu Des tra t d péril mphe non cont miné furent prélevés d n le vibul l ore lles to-sclerotiques. Il montrent des valeurs n rmales en odium, pota um l prot es. Pour la maladie d Menière les e trait vestibu l res montrent des valeurs normales pour l end l mph et ceu p ls d n la ampe l mpa ique du tour basal des aleurs normales pou la perilymph Pour les malades souffrant de neu l ome acoustique les xtraits estibulaires et du l hor ontal montrent des valeurs normales e proteines dan les trait rebrosp naux. Les an l ses biochimiques le l'oreille int rne sont utiles dan le cas d un diagnostic diffici

Studies of the human ear have involved only fluid removed from the vestibule, scala tympani of the basal turn or from the horizontal semicircular canal and have been acquired from the following sources

1 From postmortem specimens.
2. During surgical procedures.
3 Diagnostic labyrinthotomies

Early studies revealed the importance of collecting fluids without contamination by blood or tissue fluid Fluid was collected from the human inner ears through very small openings with the surrounding areas thoroughly dry and clean For example, when removing fluid from the vestibule the mucosa was elevated from the footplate of the stapes, bleeding was controlled the footplate and adjacent regions were thoroughly dried with the aspiration tube and fluid was collected by capillary attraction and gentle aspiration into a micro pipette The collection was made preferably at the level of the opening in the footplate but in no instance more than one *half millimeter into the vestibule*

When collections were made by this method the values for sodium potassium and protein in ears with otosclerosis was similar to that of perilymph for lower mammals and therefore was considered to be normal This finding is at some variance with other laboratories which have reported elevated protein values in otosclerotic ears.

The mean values for these substances in otosclerotic ears were as follows

Sodium	14	meq/L
Potassium	7	meq/L
Protein	23	mg%

Fluid removed from the vestibule by this technique from patients undergoing transmeatal labyrinthectomy for Menière's disease revealed chemical values consistent with those of normal mammalian endolymph The mean values from fifteen patients are shown below

Sodium	20	meq L
Potassium	160	meq/L
Protein	216	mg%

These findings are not surprising for histological studies have shown in Menière's disease that the endolymphatic system is greatly dilated with either the saccule or the herniated cochlear duct expanded to make contact with the footplate of the stapes.

The analysis of fluid taken from the scala tympani through the round window membrane in two patients revealed values for perilymph as follows

	Case 1	Case 2
Sodium	146 meq L	175 meq/L
P tassium	5 meq/L	m q/L
Protein	268 mg	32 mg

Thus, the fluid removed from the vestibule was endolymph and n t altered perilymph.

The removal of perilymph from the horizontal canal of patients with proven acoustic neurinomas ha revealed normal perilymph values for potassium and sodium but markedly increased protein Thi is con istent with the histological findings of a finely granular acidophilic taining precipit te in the perilymph of some ears with acoustic neurinoma The mean alues for eleven prov n acoustic neurin ma cases were as follows

Sodium	146 meq/l
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This elevated protein level was present in all eleven ears, five of which had normal protein values in the cerebrospinal fluid.

Diagnostic labyrinthotomies were performed on eleven patients in wh m it was not possible to make a definite diagnosi between Menière s disease and acoustic neurinoma In two the fluid from the vestibule was charac teristi of endolymph and the patient subsequently were treated by laby rinthectomy with relief of symptoms. F ur had greatly elevated protein levels and subsequently had successful surgical removal of acoustic neuri noma by the translabyrinthine route In five the sodium and potassium level were normal for perilymph, however protein was slightly elevated These patient are being kept under bservation

The diagnostic labyrinth t my may be helpful when otologic and neurologic examination, including audiom tric and vestibular tests, cerebrospinal fluid studies and roentgenological examination f il to provide diagnostic differentiation for the patient with suspected M nière disease or acoustic neurin ma

RÉSUMÉ

Des nal ses biochimiques d extrait d l'ore lle interne ont été faites sur des m lades souffrant d otosclérose de maladi le Menière et d neurinome ou stique Des extraits d péril mphe non contami és furent prélevés da le estibule d oreilles to-scléroliques. Ils montrent des valeurs normales en end um n potassiu t l en protéines. Pour la maladie de Me ière les extrait vestibu la res montrent des valeurs normales pour l'end lymphe t ceux pri d s la mpe tympanique du tou basal des valeurs normales pour la perilymphe Pour les malades souffrant de neurinome acoustique les extraits vestibulaires t du canal horizontal montrent des valeurs ormales en protéi es d n les e trait cérébrosp na Les analyses biochimiques d l'oreille intern sont utiles dan le cas d u diagnostic diffic le

Studies of the human ear have involved only fluid removed from the vestibule scala tympani of the basal turn or from the horizontal semicircular canal and have been acquired from the following sources

1 From postmortem specimens.
2. During surgical procedures
3 Diagnostic labyrinthotomies

Early studies revealed the importance of collecting fluids without contamination by blood or tissue fluid Fluid was collected from the human inner ears through very small openings with the surrounding areas thoroughly dry and clean For example when removing fluid from the vestibule the mucosa was elevated from the footplate of the stapes, bleeding was controlled, the footplate and adjacent regions were thoroughly dried with the aspiration tube and fluid was collected by capillary attraction and gentle aspiration into a micro pipette The collection was made preferably at the level of the opening in the footplate but in no instance more than one half millimeter into the vestibule

When collections were made by this method, the values for sodium potassium and protein in ears with otosclerosis was similar to that of perilymph for lower mammals and therefore was considered to be normal This finding is at some variance with other laboratories which have reported elevated protein values in otosclerotic ears

The mean values for these substances in otosclerotic ears were as follows

Sodium	142 meq/L
Potassium	7 meq/L
Protein	?-3 mg%

Fluid removed from the vestibule by this technique from patients undergoing transmental labyrinthectomy for Meniere's disease revealed chemical values consistent with those of normal mammalian endolymph The mean values from fifteen patients are shown below

Sodium	29 meq L
Potassium	160 meq L
Protein	1[illegible] mg

These findings are not surprising for histological studies have shown in Menière's disease that the endolymphatic system is greatly dilated with either the saccule or the herniated cochlear duct expanded to make contact with the footplate of the stapes

The analysis of fluid taken from the scala tympani through the round window membrane in two patients revealed values for perilymph as follows

	Case 1	Case 2
Sodium	146 meq L	175 meq/L
P tassium	5 meq/L	7 meq/L
[illegible] tein	208 mg	325 mg

Thus, the fluid removed from the vestibule was endolymph and not altered perilymph.

The removal of perilymph from the horizontal canal of patient with pro n acoustic neurinomas has revealed normal perilymph values for pota lum and sodium but markedly increased protein This is consistent with the histological findings of a finely granular acidophilic taining precipitat in the perilymph of some ears with acoustic neurinoma The mean values for eleven proven acoustic neurin ma cases were as f llows

Sodium	146 meq L
Potas ium	13 meq/L
Prot in	1050 mg

This elevated protein level was present in all eleven ears, five of which had normal protein values in the cerebrospinal fluid

Diagnostic labyrinthotomies were performed on eleven patients in whom it was not pos ible to make a definite diagnosis between Menière s disease and acou tic neurinoma In two, the fluid from the vestibule wa characteri tic f end lymph and the patients subsequently were treated by labyrinthectomy with relief f ymptoms. Four had greatly elevated protein les l and subsequently had ucce sful urg cal removal of acoustic n uri n ma by the translabyrinthine route In five the sodium and pota sium level were normal for perilymph however protein was slightly elevated These patient are being kept under observati n

The diagnostic labyrinthot my may be helpful when otologic and neurologic examination, including audiometric and vestibular tests, cerebrospinal fluid tudies and roentgenological examination f il t provide diagnostic differentiation for the pati nt with u pected Menière s lisease or acoustic neurinoma.

RESUME

Des an l ses b och m ques d xtrait de l'oreille interne ont ét f ites su des malade souffra t d'otosclerose d malad d Menière t d eurinome cou- st que Des extra t t périlymphe non contaminés furent prélevés dan le est bule d oreilles to-sclerot ques. Ils mont ent des valeurs normales en sodium, potas um et n prot nes. Pour la maladie de M niere le extrait estibu- laire montrent des valeurs rmales pou l ndol mphe et ceux pri dans la ampe tympanique lu tou basal des valeurs normales pour la perilymphe Pour les malades souffrant de eurinom acoustique les extraits estibulaires et du canal horizontal montrent des valeurs normales en proté es dans les trait cerebrospinan Les a alyses biochimiques d l'oreille interne sont utiles dan le cas d'un diagnostic d ff ile

Studies of the human ear have involved only fluid removed from the vestibule scala tympani of the basal turn or from the horizontal semicircular canal and have been acquired from the following sources

1 From postmortem specimens.
2. *During surgical procedures*
3 Diagnostic labyrinthotomies.

Early studies revealed the importance of collecting fluids without contamination by blood or tissue fluid Fluid was collected from the human inner ears through very small openings with the surrounding areas thoroughly dry and clean For example when removing fluid from the vestibule the mucosa was elevated from the footplate of the stapes, bleeding was controlled the footplate and adjacent regions were thoroughly dried with the aspiration tube and fluid was collected by capillary attraction and gentle aspiration into a micro pipette The collection was made preferably at the level of the opening in the footplate but in no instance more than one half millimeter into the vestibule

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The mean values for these substances in otosclerotic ears were as follows

Sodium	142 meq L
Potassium	7 meq/L
Protein	223 mg%

Fluid removed from the vestibule by this technique from patients undergoing transmeatal labyrinthectomy for Menière's disease revealed chemical values consistent with those of normal mammalian endolymph The mean values from fifteen patients are shown below

Sodium	9 meq L
Potassium	160 meq L
Protein	[illegible] mg

These findings are not surprising for histological studies have shown in Menière's disease that the endolymphatic system is greatly dilated with either the saccule or *the herniated cochlear duct expanded to make contact* with the footplate of the stapes.

The analysis of fluid taken from the scala tympani through the round window membrane in two patients revealed values for perilymph as follows

	Case 1	Case 2
Sodium	146 meq L	175 meq/L
Potassium	5 meq L	meq L
Protein	268 mg	325 mg

Thus, the fluid removed from the vestibule was endolymph and not altered perilymph

The removal of perilymph from the horizontal canal of patients with proven acoustic neurin ma has revealed normal perilymph values for potassium and sodium but markedly increased protein This i consistent with the histological findings of a finely granular acidophilic staining precipitate in the perilymph of some ears with acoustic neurinoma. The mean values for eleven proven acoustic neurin ma cases were as follows

Sod um	146 meq/L
Potassium	13 meq L
I rote n	19.6 mg

This elevated protein level was present in all eleven ears, five of which had normal protein values in the cerebrospinal fluid

Diagnostic labyrinthotomies were performed on eleven patients in wh m it wa not possible to make a definite diagnosis between Meni re s disease and acoustic neurinoma In two, the fluid from the ve tibule was charac teristic f endolymph and the patient ubsequently were treated by laby rinthectomy with relief of symptoms. F ur had greatly elevated protein levels and subsequently had succes ful urgical removal of acoustic neuri n ma by the translabyrinthine route In five the sodium and pota sium lev ls were normal for perilymph, how ver protein was slightly elevated These patients are being kept under observati n

The diagnostic labyrinthotomy may be h lpful when otologic and neurologic examination, including audiometric and vestibular tests, cerebrosp inal fluid tudies and roentgenological examination fail to provide diagnostic differentiati n for the patient with u pected Menière s disease or acoustic neurinoma

RÉSUMÉ

Des analyses biochim ques d' xtrait d l ore lle i terne ont été faites su des m lades souffra t d otosclérose de maladie de Menière et d eurinome cou stique Des tra t de perilymphe non contaminés furent prélevés da le v bule d ore lles oto-sclérotiques. Il montrent les leurs normales en od m, pot ssium et protéines. I our la maladi d M ière les extraits estibulaires mont nt des leurs normales pour l'endolymphe et ceu pri dans la rampe tympanique du tour basal des valeurs orma les pour la perilymphe Pour les malades souffra t l neuri m acoust que les xtrait estibulaires et du can l horizontal montrent des valeurs normales en protéines dan les extrait le cérébrospinau Les analyses biochimiques de l'oreille interne sont utiles da le ca d'u diagnostic diffi le

ZUSAMMENFASSUNG

Die Innenohrflüssigkeiten von Kranken mit Otosklerose, Menièrescher Krankheit und Akustikusneurinom wurden biochemisch untersucht. Reine Perilymphe aus dem Vestibulum von Patienten mit Otosklerose ergab Normalwerte von K, Na und Eiweiss. Bei der Menièreschen Krankheit ist die Endolymphe des Vestibulums sowie die Perilymphe aus der Basalwindung der Scala tympani ebenfalls normal. Bei Akustikustumoren hingegen hat die Endolymphe des Vestibulums und des horizontalen Bogenganges einen hohen Gehalt an Eiweiss, obwohl der Liquor cerebrospinalis bei diesen Kranken normal war. Aus diesem Grunde erweist sich die biochemische Analyse von Innenohrflüssigkeiten als ein praktisches diagnostisches Hilfsmittel.

H. F. Schuknecht, M.D., Dept. of Otolaryngology
Massachusetts Eye and Ear Infirmary
243 Charles St., Boston, Mass., U.S.A.

DISCUSSION

v. Schulthess: I should like to ask Mr. Schuknecht if in his cases of Menière's disease he had a relief of symptoms after creating a fistula in the footplate. Furthermore, we wish to know if the author ever could find a mixture of endolymph and perilymph which would support the hypothesis advanced by him previously that the attack of Menière is produced by a rupture of the endolymphatic system.

I. Friedmann: Congratulations to Mr. Schuknecht. We would like to know about the origin of protein. EM studies have shown certain marked degenerative changes in the epithelium of the macula in Menière's disease. That might provide the source of protein.

Meyer zum Gottesberge: The results at our laboratory in cases of Menière's disease agree completely with the findings of Mr. Schuknecht. In these cases we got mostly endolymph by puncture through the oval window. We have no experience in cases of acoustic neurinoma.

G. Dohlman: I would like to ask Mr. Schuknecht if he has taken samples of perilymph with his excellent sampling technique in the period when one would expect the electrolyt changes in connection with Menière's attack. I realize the difficulty of getting the perilymph from the pertinent area but in cases with periods of low bone impairment, where theoretically you would expect a leak of endolymph through a rupture at the helicotrema, it would perhaps be possible to see some potassium increase in the perilymph of scala tympani.

L. Rüedi: I would like to confirm the findings in Menière's disease. We found also in the liquid gained through a fistula in the footplate of the stapes K and Na values typical for endolymph. On the other hand, through the round window we got in these cases K and Na values corresponding to perilymph.

H. F. Schuknecht (Reply): It is gratifying to learn that Mr. *Meyer zum Gottesberge* and Mr. *Rüedi* have confirmed the chemical findings of vestibule fluid of ears with Menière's disease in studies performed in their laboratories. Mr. *von Schulthess* and Mr. *Dohlman* have commented on the question of the mixing of

fluids (perilymph and endolymph) during diagnostic labyrinthectomy. It is true that one theory for the etiology of the episodic vertigo in Menière disease is rupture of the endolymphatic system. Our patients, however, had almost no reaction to diagnostic labyrinthectomy and we can only assume that the removal of fluid from the vestibule did not create mixing of fluids or severe distortion of the membranous labyrinth. Collapse of the dilated saccule of course must take place. The cause of the low frequency deafness in Menière disease continues to be a mystery—and possibly even more so since Mr Kimura of our laboratories demonstrated that degenerative lesion of the apical region often follows destruction of the endolymphatic sac in the guinea pig. Mr *Friedmann* the explanation for the elevated protein of the perilymph of patients with acoustic neurinoma is also unknown. The fact that this elevation may occur in the presence of normal cerebrospinal fluid protein values indicates, however, the diagnostic value of the perilymph tap in difficult diagnostic problems.

ZUSAMMENFASSUNG

Die Innenohrflüssigkeiten von Kranken mit Otosklerose Menièrescher Krankheit und Akustikusneurinom wurden biochemisch untersucht Reine Perilymphe aus dem Vestibulum von Patienten mit Otosklerose ergab Normalwerte von K, Na und Elweiss Bei der Menièreschen Krankheit ist die Endolymphe des Vestibulums sowie die Perilymphe aus der Basalwindung der Scala tympani ebenfalls normal Bei Akustikustumoren hingegen hat die Endolymphe des Vestibulums und des horizontalen Bogenganges einen hohen Gehalt an Eiweiss obwohl der Liquor cerebrospinalis bei diesen Kranken normal war Aus diesem Grunde erweist sich die biochemische Analyse von Innenohrflüssigkeiten als ein praktisches diagnostisches Hilfsmittel

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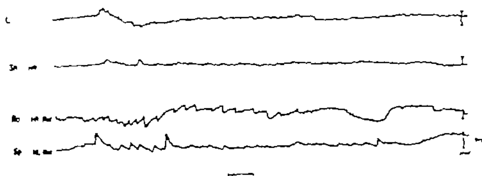


Fig. 1

movement during the stimulus and he usually was not asked to attend to his experience This differs from the pilot of a plane who frequently ini tiates the stimulus with his own controls and then must purposely suppress or ignore misleading vestibular input The habituation studies I'm about t describe deal with the earthbound simulation of a rotating space station, and in these studies the subject himself initiated the stimulus each time it occurred by a *voluntary* movement of his head.

Rotating space stations r under consideration because rotation is the simplest means of producing an artificial gravity when a person is in a weightless condition The problem with a rotating space station lies in the fact that many people become motion sick while living in an enclosed rotating chamber and the higher the rate of rotation, the greater is the tendency to become sick. Unfortunately very low rates of rotation require ery large radii to produce an artificial gravity of 1 g-unit For example 2 rpm requires an 800-ft radius to produce 1 g unit, whereas 8 rpm only requires a 50-ft radius. In the process of determining how people adjust to a continuously rotating en ironment, we have found some interesting modifications of vestibular reaction which I'm going to describe today

W ha done experiments in which rates of rotation were varied be tween 1 and 10 rpm with men li ing in the rotating room for as long as several weeks (Graybiel *et al* 1960 Guedry 1965 Guedry & Graybiel 1962) For some tim after rotation commences, each head movement in duces an unusual sensation. For example rotating the head forward produces a sensation, not of forward rotation, but of lateral rotation of the head and body Nystagmus in plane at right angles to the head movement may also be recorded. As few as three or four head movements while rotating at 10 rpm will make ick some sensiti e men. However most of our subject ha e shown an ability to habituate to this environment This habituation becomes manifest in several ways. During prolonged exposure most men have reported that the misleading sensations, the nystagmus, the nausea and motion sickness diminished or disappeared. However afte

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SOME VESTIBULAR PROBLEMS RELATED TO ORIENTATION IN SPACE

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Aircraft and spacecraft introduce unnatural combinations of vestibular and visual stimuli Many of these situations produce spatial disorientation and performance degradation which can be anticipated by knowledge of the mechanics of vestibular stimulation Experiments to test predictability of reactions to unnatural vestibular stimuli have contributed to current knowledge of vestibular function Some of these experiments are reviewed to illustrate methods employed for the assessment of vestibular function and to illustrate implications of the results for spatial orientation and theory of vestibular function

INTRODUCTION

Aircraft and spacecraft are capable of producing vestibular stimulation which can be highly disturbing to flight personnel I am going to review briefly some of our research in three general problem areas (A) Habituation to unusual vestibular stimulation (B) interactions between linear and angular accelerations in controlling the dynamics of spatial orientation and (C) visual acuity during strong vestibular stimulation

RESEARCH ON VESTIBULAR FUNCTION IN RELATION TO PROBLEMS OF AEROSPACE FLIGHT

A *Habituation to unusual vestibular stimulation* has been revived as an area of special interest since the advent of the space age Most men are habituated to the vestibular stimulation which accompanies natural movement and even the unnatural movement of our many land vehicles The reflex activity and sensations which are set off in these situations are appropriate and hence beneficial to coordinated movement However unusual maneuvers of certain air and spacecraft introduce vestibular stimulation which is sometimes incapacitating

There is a distinction which I think is important between the habituation I ll describe today and a number of recent habituation studies Many habituation studies have consisted of repetitive passive rotation of a restrained animal or man. The test subject was not trying to control his

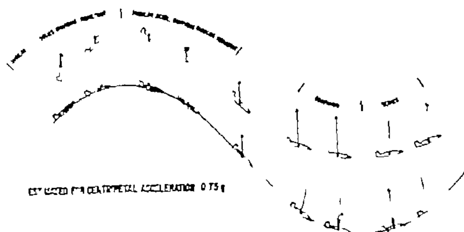


FIG. 6.

less steep climb than is actually occurring, and hence they tend to pull up too fast. Here the magnitude of the resultant force is probably so great as to override angular acceleration stimulus to the canals and the misleading direction of the resultant force misleads the pilot

C. *The ability to see during and after recovery from a turn or spin* is the third area of experimentation I'd like to describe. During a turn or spin, vestibular nystagmus may aid visibility of the earth, but it will interfere with visibility of flight instruments in the cockpit Cessation of a rapid spin or spiral of several turns can produce a false sense of reversed spinning and blurred vision of cockpit and earth, all of which jeopardizes aircraft control (Melvill Jones, 1957) The question is What is the strength of the vestibular stimulus required to degrade cockpit vision, and how much do people differ in this regard?

To investigate this, we used pilot candidates, all with good static visual acuity and required them to identify sets of visual targets graduated in size during and after prolonged angular acceleration (Guedry 1967) Prolonged accelerations were used to provide time for visual judgments.

Some of the results are shown in Fig. 6, where arrows designate the beginning and end of a 12 second interval of 30 deg/sec² angular acceleration Dots below the individual nystagmus tracings show when the subject signaled loss of sets of visual targets.

Just after the last dot to the right designating loss of the largest target set an abrupt increase in nystagmus amplitude occurs. This amplitude change seems to indicate the point of surrender of voluntary efforts to maintain visual suppression of nystagmus, and it is not accompanied by a comparable increase in nystagmus slow phase velocity However before this amplitude change there are successive step-like increases in slow phase velocity which seem to correspond to the loss of successively larger target sets.

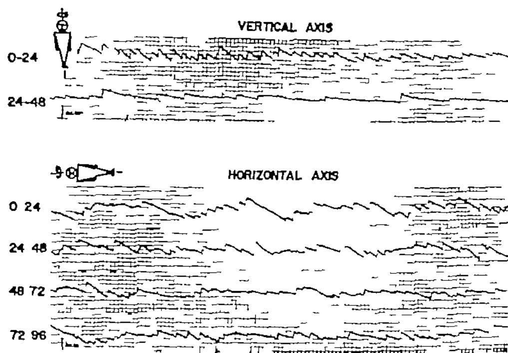


FIG 4

each case (Guedry 1965) This response about the horizontal axis is accompanied by a sensation of continuous rotation in normal men when the rotation rate is 10 rpm or less. In people without inner ear function neither the continuous sensation of rotation nor the unidirectional nystagmus occurs When the rate of rotation is 30 rpm, the unidirectional nystagmus disappears after the angular acceleration, and the sensations reported by normal men are the same as those reported by men without labyrinthine function (Correia & Guedry 1966) From this and related research (Benson & Bodin, 1965 Benson & Whiteside 1961 Guedry 1966 Guedry & Harris, 1963 Lansberg *et al.*, 1965) I have become increasingly convinced that an understanding of dynamic spatial orientation requires consideration of the *combined* action of canals and otoliths and that the separate consideration of the function of canals and otoliths can be misleading

Now let us look at a situation in flight illustrated in Figure 5 which is probably influenced by these effects In a climb and dive maneuver the resultant at the beginning of the pushover shifts in a direction which would make the pilot experience a nose-up attitude greater than is actually the case but here the angular acceleration would contraindicate this change in attitude Hence the perceptual error at the beginning of the maneuver should be diminished However as the pilot continues the pushover maneuver the resultant shifts to make the pilot experience a steeper dive than is occurring and furthermore now the semicircular canal information confirms the change in resultant Hence the perceptual error could be great In fact pilots don t have trouble in the beginning of the pushover but they do experience a too-steep drive In the pullup they experience a

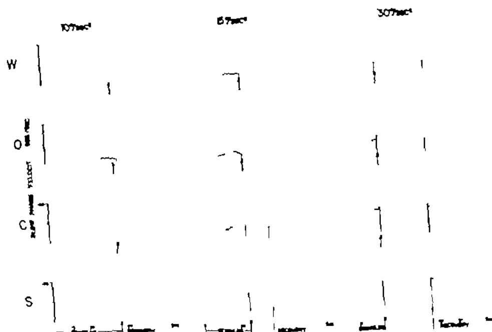


FIG. 8.

proceeded in step-like fashion. Apparently visual suppression could effect a step-like drop in nystagmus velocity only after vestibular input declined to a certain level. In other words during the recovery when eye velocity declined to permit registration of some minimal visual pattern visual suppression could effect a step-like decline in nystagmus slow phase velocity

Fig. 8 i also sufficient to show the magnitude of individual differences mong pilot candidates with equal nd good static visual acuity Subject *S* with the weakest stimulus had much more nystagmus than subject W with the strongest stimulus, and the visual performance of *S* with the weakest stimulus was inferior to that of W with the strongest stimulus. Considering the 10 deg/sec² stimulus, W maintained essentially normal vision while *S* became virtually blind for visual detail

Further checks of 17 subject revealed that there were significant correlations between visual acuity scores and nystagmus scores and that these were about equivalent to correlations between two sets of nystagmus scores. Nystagmus recorded in darkness was significantly correlated to nystagmus recorded in the light and both were correlated to visual acuity scores. In other words, the scores of n individual on one of these measures could be used to predict fairly well his scores on the other measures

Th plots presented in Fig. 8 were made by an electromechanical slope computer we re dev loped (Guedry & Turnipseed, 1967) Recently there

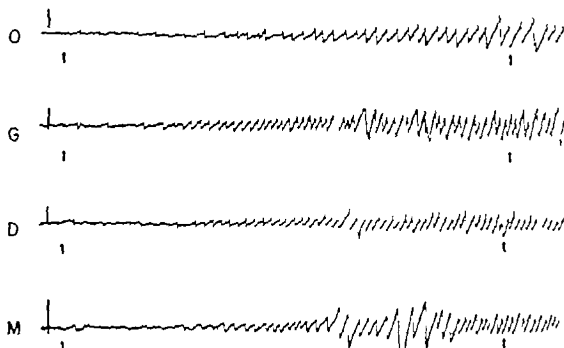
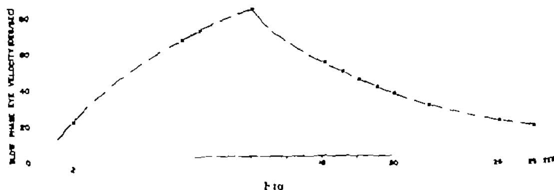


Fig 6.

The average rise curve of eye velocity plotted with respect to time during the visual task differs in shape from the negative exponential rise curve expected from mechanics of the cupula endolymph system as described by van Egmond *et al* (1949) This is shown in Fig 7 where the dots are average eye velocities obtained during a 30 deg/sec- stimulus Individually scored records suggest that this pronounced departure from the "expected" curve is attributable to the averaging of step-like increments in velocity which in turn were accentuated by the visual suppression

These step-like rises in slow phase velocity can be seen in Fig 8 which shows individual results of subjects W O C and S during and after angular accelerations of three magnitudes These step like increases in nystagmus velocity seem to mark levels of vestibular activity which overcome limits of visual suppression for different size targets The nystagmus decay also



Fig

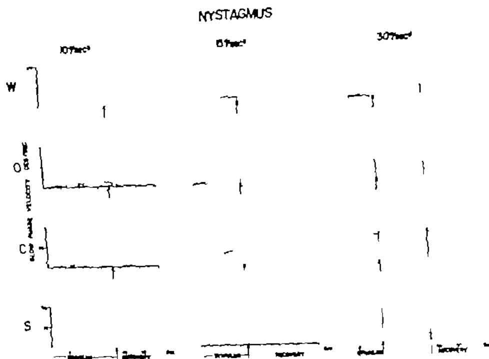


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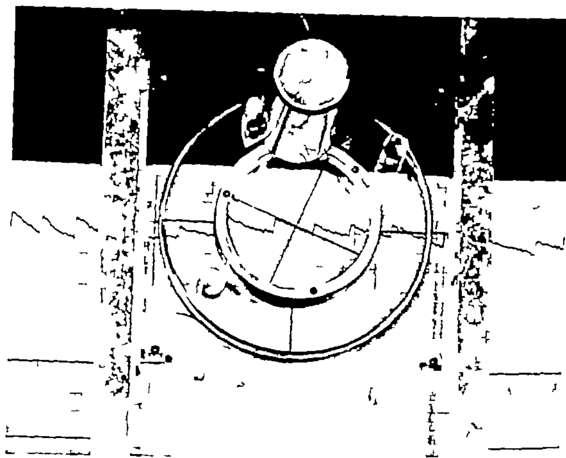


Fig 9

seems to be an increase of interest in the scoring of nystagmus and for this reason I ll describe this device we re using very briefly

As the dial shown in Fig 9 is turned until the crosshairs and nystagmus slope match a potentiometer supplies a voltage which is converted by a function generator into angular velocity Another potentiometer supplies a voltage proportional to time A digital voltmeter prints out the nystagmus velocity and time of each beat while an X Y plotter plots the analog display The individual graphs present in Fig 8 were obtained directly from the X Y plotter Hence our records are measured tabulated and plotted much faster than measurement alone was previously accomplished (See also Benson & Stuart 1966)

RÉSUMÉ

L avion et la cabine spatiale nous ont confrontés avec des combinaisons in habituelles de stimulus vestibulaires et visuels. Ces situations causent fréquem ment une désorientation et une dégradation dans les performances qu on peut prévoir par la connaissance du fonctionnement de l appareil vestibulaire L étude des réactions à une stimulation vestibulaire inhabituelle a complété nos con

naissances actuelles du ystème vestibulaire Qu lques unes de ces expériences concernent des combinaison d accélération liné ire et angulaire Celles-ci sont util sées dans l'examen estibulaire afin de trouv r leurs implication quant à l'orientation dans l'espace t quant à la théorie de la fonction vestibulaire

ZUSAMMENFASSUNG

Flugzeuge und Raumschiffe erzeugen unnatürliche K mbinationen vestibulärer und Schreize Viele dieser Bedingungen I d begleitet von räumlicher Disorien t eru g nd verri gerter Leistungsfähigkeit, die vorausgesehen werden können wenn der Mechanismus der estibulären Funktion bekannt ist Einige dieser E perimente die ich auf spezielle Kombinationen linearer und Winkelbeschleu n gungen bezogen, werd n untersucht um die Methoden der Auswertung vesti bulärer Funktion und die Folgerungen der Ergebni se für die räumliche Orien t erung und die Theorie der vestibulären Funktion zu illustrieren.

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DISCUSSION

M Burgeat I was very much interested by Mr Guedry s communication. Indeed as far as nystagmus is concerned, we have found also on small animals that after intermittent rotation around the vertical axis of the labyrinth the nystagmus response shows a very important diminution which takes several days to recover if it does Also with the financial help of the french national defense office we have built a machine in order to study more precisely these phenomenon by rotation in the 3 axis and recording of different biological responses and physical parameters at the same time

L B W Jongkees I congratulate Mr Guedry on his remarkable contribution. I have some questions and remarks

(1) The adaptation to complicated Coriolis stimuli has already been described by Groen before the Collegium Groen found a great habituation to the movements of ships at sea and called this "pattern building"

(2) Could Mr Guedry comment on Benson s slosh" theory?

(3) The equation for endolymph-cupula movements proposed by Egmond, Groen & Jongkees, is only valuable during the first seconds of stimulation. After about 15 sec the canal stimulation has completely stopped The effects found during constant acceleration must be due to visual stimulation a canalicular factor in them is impossible

F E Guedry (Reply) to Dr *Burgeat* I am quite interested in the work you described related to our experiments. I believe that there may be an important distinction between (1) repetitive vestibular stimulation of a restrained animal or man who does not produce the stimulus by his own actions and (2) our experiments in the rotating room in which subjects introduced the stimulus by voluntary head movements. This may produce different results than repetitive passive stimulation

to Mr *Jongkees* Regarding his comments on adaptation I am familiar with Groen s "pattern copy" hypothesis to explain sea legs" etc It seems to me that our results are in support of this general theoretical position and our records of nystagmus produced by head movements after subjects leave the rotating room are objective support

In regard to Mr *Jongkees* comment on the Benson slosh" theory—this refers to one of several ideas Alan Benson had in regard to possible explanations of the prolonged unidirectional nystagmus present during rotation about a horizontal axis. Basically the idea is that a difference in specific gravity of endolymph and perilymph could cause a pumping action by virtue of a traveling deformation around the membranous canal. In an experiment involving record

ings in the vestibular nuclei of cats from units which seemed to have their origins in the horizontal canals, Melvill Jones, Denson and I found evidence which seemed to support this notion. However all of us still regard this idea as speculation.

In regard to the fact that the torsion pendulum analogy does not predict very well with prolonged estibular stimulation, i.e. more than 10 sec, I am in agreement. Subjective sensations of rotation decline during constant angul r accelera tion and show earlier departures from the theoretical curve than do nystagmus responses. I have reported experiments which illustrate these departures from the "torsion pend lum theory

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NYSTAGMIC CORIOLIS REACTION IN THE CAT

I Preliminary Report

C. FERNÁNDEZ, M D and M VALENTINUZZI M D

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A series of cats with normal ears and with unilateral labyrinthectomy were exposed to Coriolis acceleration by simultaneous rotations of constant angular velocity about a vertical and horizontal axis In both sets of animals, the results were in agreement with predictions formulated by the labyrinthine kinematics of Coriolis acceleration The recordings showed that in both horizontal and vertical leads two reversals in the direction of nystagmus occurred for each oscillation of the Coriolis acceleration The infra red films demonstrated that the direction of nystagmus changed orderly for each oscillation of Coriolis acceleration A phase difference between this oscillation and reversals of nystagmus was found The phase difference was shifted as a function of angular velocity about the horizontal axis.

The kinetics of the cupula-endolymph system under Coriolis acceleration has been described in detail by a number of investigators (Schubert, 1932 Meda 1952 Bornschein & Schubert 1958 Guedry & Montague 1961 Hixson Niven & Correia, 1966 Valentinuzzi 1967 and others) The theoretical considerations have predicted and then confirmed experimentally the subjective and nystagmic aspects of the vestibular Coriolis reaction in man In the guinea pig, Bornschein & Schubert (1958) demonstrated similar nystagmic effects The experiments reported here were designed for the purpose of observing the vestibular Coriolis reaction in normal and in unilateral labyrinthectomized cats In this preliminary report the evaluation of the findings is presented in a qualitative form

METHODS

The experiments were carried out in eleven normal and in ten unilateral labyrinthectomized cats The testing of the latter was done after the vestibular disorder had compensated that is, in 30 or more days after the opera

This work was supported by Grant NB-1330-10 from NIH and AF 41(609) 2768 from School of Aviation Medicine San Antonio Texas.



Fig 1 The pper photograph sho k ll f th eat with impla ted lectrodes f recording horizontal and ertical components of nystagmus G ground lectrode The lo er photograph shows nimal with perma ently impla ted electrodes and pl g-in. Insert dra ing. The screw S is made of ylon (2.7 mm l diameter) with central perforation int which solated lead is inserted (plastic Vl yl coating) The tip, A of isol ted lead, L, is made of silver wire which f ts tightly t the screw perforat on. T ensure permanency of cement ttachme t it l d isabl t reinf rce it with two metal screws. It is essential that the individual leads lw y be soldered t the same pin of the socket

tion. Silver wire electrodes were implanted in th xternal canthi of both orbits and in the upper and lower ridges of the right orbit (Fig 1) for recording the horizontal and ertical components of nystagmus respectively The isolated lead and reference lead were soldered to a 5-pin subminiature socket which was cemented to the skull. Th skin was sutured ove the leads and around the socket These electrodes remained in place for months without complications. The corneoretinal pot ntial and angular velocity of the rotating devices were recorded by conventional DC coupling methods (Offner Dynograph, Type R model) We found that under our experi-

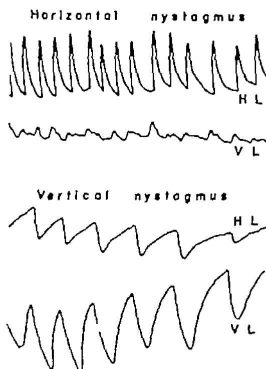


FIG. 2. Records of a horizontal and vertical nystagmus as recorded by horiz ntal (*H.L.*) a d v rtical (*V.L.*) leads. The recording of a pure h rizontal nystagmus by the vertical le ds may be du to a numbe of auses uch as unfavorable ori ntation f the ocular bioelectric field relative t the recording electrodes. Similar causes may result in recording v rtical nystagmus by the h rizontal lead

mental conditions, the vertical leads recorded distinctly a pure horizontal nystagmus although its amplitude was small Similarly pure vertical nystagmus had been recorded distinctly by horizontal leads (Fig 2)

The cat was immobilized in an animal box as described elsewhere (Henrikson Fernández & Kohut 1961) The box was fixed to the ring of a superstructure mounted upon a turntable (Fig 3) so that the plane of the horizontal canal was oriented on the Earth horizontal plane The three cardinal axes, relative to the head of the animal intersected approximately at a point midway between the two ears The turntable and ring of the superstructure rotated independently and simultaneously in a clockwise or counterclockwise direction according to a pre set program The turntable rotated about the y axis while the ring of the superstructure rotated about the ~ axis of the cat In static conditions during rotation of the ring both y axis and x-axis of the cat were continuously changing their spatial orientation relative to the respective axes of the turntable

The testing of the cat consisted of three stages First, the turntable was rotated at constant angular velocity ω_p for one minute before starting rotation of the ring about the axis This interval was considered sufficient to eliminate any effects p oduced by the initial acceleration of the turntable Second, the ring of the superstructure was rotated at constant angular velocity ω_n for ten complete turns about the -axis Third the turntable

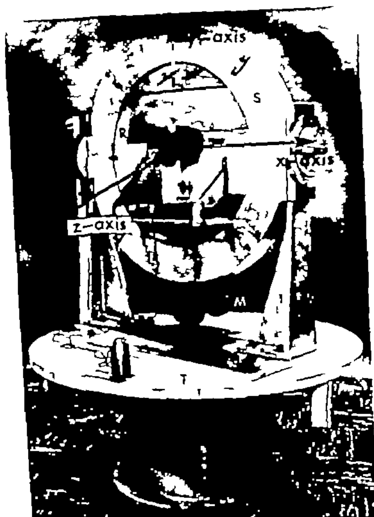


Fig. 1. Photograph of the rotatory device with cat mounted it. The t rotable, T is mounted on larg diameter shaft which i directly coupled t DC torque motor and DC tachometer (Inland Controls, Precision R t T bl System, Model 722) The superstructure, S, contains rotating ring, R which is coupled by belt t DC motor M The cat is mounted on platf rm ttached to R The leads, L, re connected t the shaft of the turntable and by slip ri gs t the input leads of the Dynograph. The three card nal xes are dra relativ t the cat' head. The y-axi i coincident with the y-axi of the turntable At rest, the horizontal xz plane lies on the Earth-horizontal plane Rotation bout y-axi is lw y referred to the y-a is f the turntable while rot tion about the -axis is al ys referred to -axis of the cat.

continued rotating about the y-axis for on additional minute. The testing was don in total darkness. Th nimal was not tested oftener than every eight days and each testing period consisted of three to six runs each, repeated at 15 minute intervals In these sessi ns either the angular velocity ω_y wa maintained constant while ω was varied, or vice versa, or

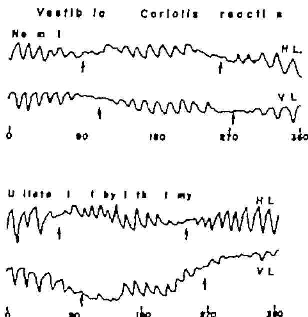


FIG. 5 Nystagmi Cori lis re tion. *H.L.*, h izontal leads *V.L.*, vertical leads. The cat w s rotated clockwise at ω = 80 deg ec and ω = 28 deg/sec Th c t with ll teral labyrinthect my wa lso rotated clockwise at ω = 80 deg sec a d ω = 30 deg/sec The arrows point to the area where reversals f nystagmus occu Th ph se difference between rev rsals from horiz ntal nd ertical leads i dem n trated The pattern of nystagmu of the normal animal i imila to that f the cat with nilateral labyrinthectomy The reversals in the vertic l l ad re lagging the revers ls of the horizontal le d

Vestibular Coriolis reaction

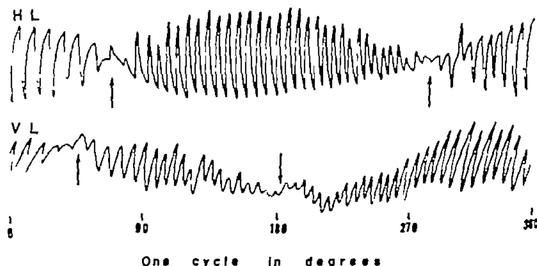


FIG 6 Records illu t t g riety of y t gmic Corioli reacti R t ti n w clockwise abo t both y-axi d -a l (ω₁ = 80 deg sec ω = 30 deg sec *H.L.*, horizont l leads *V.L.*, ertical l d Th figure sh w th ny t gmu f th th rd vele abo t -a l The arrows point t w d th rea of rev rsal In thi run th reversal f the horizo tal lead are laggi g th re rsals of th rti l l ads

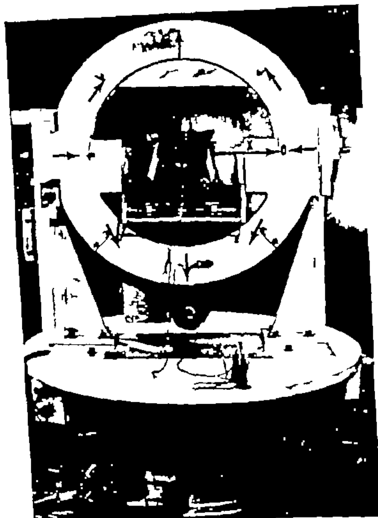
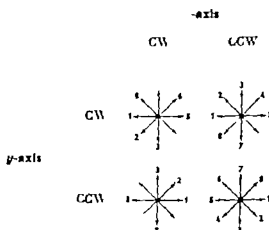


Fig. 7. Vectorial representation of the periodic Coriolis star nystagmus. The cat was rotated clockwise about both y-axis and x-axis (ω_y 80 deg/sec, ω_x = 30 deg/sec). The arrow X indicates the x-axis of the cat. The vectorial presentation of nystagmus relative to the head of the cat is indicated by arrows on the frame of the superstructure. As the x-axis rotates clockwise the direction the sequential change in the vectors is counterclockwise. Notice that magnitude of the vectors are equally represented although the oblique vectors may be somewhat smaller.

towards the forehead of the cat respectively. In between these positions the direction of the nystagmus was oblique as shown in the figure. No rotatory component was ever observed in the infra red films. The vector of the periodic Coriolis star nystagmus changed according to clockwise or counterclockwise rotation about the y-axis or x-axis, as shown in Table 1. When the rotation about both y-axis and x-axis was clockwise, the nystagmic vector rotated counterclockwise. A clockwise rotation about the y axis and

TABLE 1 *Vectorial presentation of the fast phase of the periodic Coriolis-like nystagmus as a function of simultaneous rotation about the y-axis and -axis*

The frame of reference is the head of the cat Then numbers indicate the sequence of nystagmic vectors as the cat rotates 360 deg. about the -axis. The equal magnitude of the vectors is arbitrary



counterclockwise rotation in the axis produced clockwise rotation of the vector The table indicates the sense of the nystagmic vector for the four combinations of rotations about *y* axis and axis The form horizontal or vertical nystagmus, the direction and the change of the nystagmic vector can also be determined on the recordings.

The first reversal of the nystagmus during a complete cycle of the ring of the superstructure occurred between 0 and 180 while the second reversal was found between 180 and 360 For one set of conditions, the phase difference, φ between 0 and first reversal was of about the same magnitude as that between 180 and second reversals The value of φ however changed as a function of ω that is, for a fixed value of ω_r, the phase angle, φ was displaced progressively with increased value of ω (Fig 8) This shift appeared in both the horizontal and the vertical leads On the other hand, for a constant value of ω, the increase of ω_r was associated with no change of φ (Fig 9)

The two sets of leads recorded eye movements of similar pattern that is, between two consecutive reversals, the amplitude of nystagmus was first small increased to a maximum and then diminished until it disappeared The infra red film showed eye movements of about the same amplitude in the horizontal and vertical planes while oblique jerks were somehwat of smaller amplitude This pattern was repeated from one cycle to another and under all combinations of ω_y and ω which were used

The frequency of the nystagmus in both leads seems to be a function of both ω_y and ω_r. Apparently the frequency increased with ω ω_r.

The velocity of slow phase of nystagmus appeared as a linear function

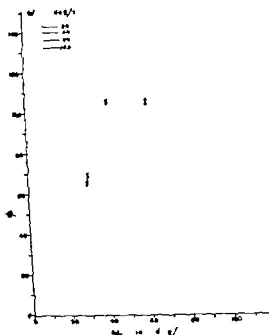


FIG. 8. Phase difference φ between Coriolis acceleration and reversal of nystagmus plotted as a function of ω_r. The measurements were made in the records from horizontal leads. For each cycle about the z axis, the phase differences of first and second reversals to 0° and 180° respectively were measured and averaged. These averages of the ten runs of each session were added and the average calculated. The latter is represented by the point on the graph. The data for various values of ω_r are represented by symbols. The figure illustrates the trend of φ to increase as ω increases.

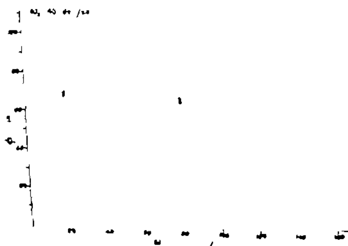


FIG. 9. The phase difference, φ, of reversal of nystagmus plotted as function of ω_r. The values were calculated as described in Fig. 8. There is scattering of the points, but the general trend is toward constant value including the highest value of ω_r.

of ω_y for values up to 100 deg/sec. No higher values have been used because of instrumental limitations. So far the data indicated a non linear relationship between speed of slow phase and ω_z.

DISCUSSION

The experimental findings presented in this preliminary report are predictable from the kinematics of the cupula-endolymph system exposed to rotation about two orthogonal axes. We only like to emphasize a few points in order to understand the stimulation under our experimental conditions.

The theoretical considerations postulate that simultaneous rotation at constant angular velocity about a y axis and a axis results in a Coriolis acceleration of different magnitudes around the circumference of the endolymphatic rings. Thus, the endolymph must move according to the effective resultant of the inertial torque. The theory has predicted that the resultant is an oscillation following a sine function in the horizontal canals while in the vertical canals follows a cosine function. Consequently the endolymphatic currents must follow similar functions. The magnitude of the effective resultant torque is a function of $_y$ (Bornschein & Schubert, 1958; Valentinuzzi, 1967). If the cupula-endolymph system follows the oscillation of the torque, then the endolymphatic currents must change their direction twice during one complete oscillation of the resultant. Accordingly the nystagmus associated with the displacements of the cupula-endolymph system must reverse its direction twice during one oscillation of the resultant. Our experimental findings clearly demonstrated that this was the case. Furthermore, the theory also predicts that the duration of one oscillation of the resultant torque is a function of and therefore, during this time only two reversals should occur. The experimental findings confirmed this prediction since an increase of ω up to 100 deg/sec was consistently associated with only two reversals of nystagmus during any complete rotation about the axis.

The theory that the cupula-endolymph system of the semicircular canals behaves as a highly damped torsion pendulum (Steinhausen, 1931; van Egmond, Groen & Jongkees, 1949; Groen, Löwenstein & Vendrik, 1952) accounts for the phase difference between reversals of nystagmus and oscillation of Coriolis acceleration. The increase in this phase difference as function of ω still requires further analysis.

The estimates of the intensity of the nystagmic Coriolis reaction as determined by the speed of the slow phase of nystagmus indicated a nonlinear relation with ω for the range used in our experiments. Because of instrumental limitations we have no information about intensity of nystagmus for values of ω higher than 100 deg/sec. On the other hand, the data showed that the speed of the slow phase followed a linear relation to ω_y.

The form and direction of nystagmic Coriolis reaction is also predicted from the theory. Let us consider the x-axis of the animal (Fig. 7) passing

through 0 at constant angular velocity in a clockwise direction If the damping of the cupulo-endolymph system is considered, then the kinematics of Coriolis acceleration *shows a torque* acting upon the endolymphatic ring producing an ampullopetal flow in the right horizontal canal and an ampullo-fugal flow in the left horizontal canal Therefore the nystagmus must be toward the right of the animal as shown by the infra-red film The same theoretical considerations about the torque in other positions predict accurately the direction of nystagmus. These calculations are considerably facilitated by using models or anatomical preparations of the cat's skull The analysis of the kinematics of Coriolis acceleration acting upon the vertical canals also predicts the sequential change in direction of the "periodic Coriolis star nystagmus" from a horizontal to a vertical direction. This was demonstrated in the infra-red films

The pattern of electronystagmogram regarding amplitude of nystagmu lso can be predicted from the kinematics of Coriolis acceleration The amplitude measurements *of nystagmus between two reversals as shown for* instance, by the horizontal leads of Fig. 6 revealed a progressive increase *to a maximum and then decrease until* it disappeared. The increase and fading of the amplitude of the recordings are due to displacement of the cupula-endolymphatic ring and to the change in direction of the bioelectric field as the nystagmic jerks approach and then pass the horizontal plane of the cat. The horizontal electrodes only record the horizontal component of this bioelectric field.

It was not urprising to find that the "periodic *Coriolis* star nystagmus" of cats with unilateral labyrinthectomy was similar to that of normals. The similarity is related t the neural mechanism underlying vestibular com*pensation which was already established* in our animals. *Under this* condition the vestibular reaction produced by stimulation of the remaining labyrinth can hardly be differentiated *from that of a normal cat.*

As a last commentary we would like to point out that the role of the otolithic system in the nystagmus of the vestibular Coriolis reaction is not known. The magnitude of the Coriolis acceleration under our experimental conditions seems to be small as compared with the acceleration of gravity The same conclusion was reached by Guedry & Montague (1961) in their experiment with man. This speculation however requires further experimentation.

RESUME

L série de chats avec oreilles normales et vec labyrinthectomie unilatérale ont ét soumis un *accélération de Coriolis* par rotations simultanées vélocités ngulaires consta tes autour d'un axe vertical et d'un axe horizontal. Dans les deux groupes d'animau les résultats nt été d accord avec les *prédictions formulées* par la cinématique de l'accélérati n de Coriolis. Les enregistrements ont montré dans les électrodes horizontales et verticales deux renversements d la direction du nystagmus *pour chaque oscillation de l'accélération* d Coriolis. Les

of ω_y for values up to 160 deg/sec No higher values have been used because of instrumental limitations So far the data indicated a non linear relationship between speed of slow phase and ω_x.

DISCUSSION

The experimental findings presented in this preliminary report are predictable from the kinematics of the cupula-endolymph system exposed to rotation about two orthogonal axes. We only like to emphasize a few points in order to understand the stimulation under our experimental conditions.

The theoretical considerations postulate that simultaneous rotation at constant angular velocity about a y axis and a -axis results in a Coriolis acceleration of different magnitudes around the circumference of the endolymphatic rings Thus the endolymph must move according to the effective resultant of the inertial torque The theory has predicted that the resultant is *an oscillation* following a sine function in the horizontal canals while in the vertical canals follows a cosine function Consequently the endolymphatic currents must follow similar functions The magnitude of the effective resultant torque is a function of ω_y ω (Bornschein & Schubert, 1958 Valentinuzzi, 1967) If the cupula-endolymph system follows the oscillation of the torque, then the endolymphatic currents must change their direction twice during one complete oscillation of the resultant Accordingly the nystagmus associated with the displacements of the cupula-endolymph system must reverse its direction twice during one oscillation of the resultant Our experimental findings clearly demonstrated that this was the case Furthermore, the theory also predicts that the duration of one oscillation of the resultant torque is a function of and therefore, during this time only two reversals should occur The experimental findings confirmed this prediction since an increase of up to 160 deg sec was consistently associated with only two reversals of nystagmus during any complete rotation about the axis

The theory that the cupula-endolymph system of the semicircular canals behaves as a highly damped torsion pendulum (Steinhausen 1931 van Egmond, Groen & Jongkees, 1949 Groen, Löwenstein & Vendrik, 1952) accounts for the phase difference between reversals of nystagmus and oscillation of Coriolis acceleration The increase in this phase difference as function of ω still requires further analysis

The estimates of the intensity of the nystagmic Coriolis reaction as determined by the speed of the slow phase of nystagmus indicated a nonlinear relation with ω for the range used in our experiments Because of instrumental limitations we have no information about intensity of nystagmus for values of ω higher than 100 deg/sec On the other hand the data showed that the speed of the slow phase followed a linear relation to $_r$

The form and direction of nystagmic Coriolis reaction is also predicted from the theory Let us consider the x axis of the animal (Fig) passing

through 0 at constant angular velocity in a clockwise direction. If the damping of the cupulo-endolymph system is considered, then the kinematics of Coriolis acceleration shows a torque acting upon the endolymphatic ring producing an ampullopetal flow in the right horizontal canal and an ampullo-fugal flow in the left horizontal canal. Therefore the nystagmus must be toward the right of the animal as shown by the infra-red film. The same theoretical considerations about the torque in other positions predict accurately the direction of nystagmus. These calculations are considerably facilitated by using models or anatomical preparations of the cat's skull. The analysis of the kinematics of Coriolis acceleration acting upon the vertical canals also predicts the sequential change in direction of the "periodic Coriolis star nystagmus" from a horizontal to a vertical direction. This was demonstrated in the infra-red films.

The pattern of electronystagmogram regarding amplitude of nystagmus also can be predicted from the kinematics of Coriolis acceleration. The amplitude measurements of nystagmus between two reversals as shown for instance by the horizontal leads of Fig. 6, revealed a progressive increase to a maximum and then decrease until it disappeared. The increase and fading of the amplitude of the recordings are due to displacement of the cupula-endolymphatic ring and to the change in direction of the bioelectric field as the nystagmic jerks approach and then pass the horizontal plane of the cat. The horizontal electrodes only record the horizontal component of this bioelectric field.

It was not surprising to find that the "periodic Coriolis star nystagmus" of cats with unilateral labyrinthectomy was similar to that of normals. The similarity is related to the neural mechanism underlying vestibular compensation which was already established in our animals. Under this condition the vestibular reaction produced by stimulation of the remaining labyrinth can hardly be differentiated from that of a normal cat.

As a last commentary we would like to point out that the role of the otolithic system in the nystagmus of the vestibular Coriolis reaction is not known. The magnitude of the Coriolis acceleration under our experimental conditions seems to be small as compared with the acceleration of gravity. The same conclusion was reached by Guedry & Montague (1961) in their experiments with man. This speculation however requires further experimentation.

RÉSUMÉ

Une série de chats avec oreilles normales et avec labyrinthectomie unilatérale ont été soumis à une accélération de Coriolis par rotations simultanées à vélocités angulaires constantes autour d'un axe vertical et d'un axe horizontal. Dans les deux groupes d'animaux les résultats ont été d'accord avec les prédictions formulées par la cinématique de l'accélération de Coriolis. Les enregistrements ont montré dans les électrodes horizontales et verticales deux renversements de la direction du nystagmus pour chaque oscillation de l'accélération de Coriolis. Les

prises cinématographiques infra-rouges ont démontré que la direction du nystagmus changeait d'une façon ordonnée pour chaque oscillation de l'accélération de Coriolis. On a trouvé une différence de phase entre cette oscillation et les renversements du nystagmus. La différence de phase était décalée en fonction de la vélocité angulaire autour de l'axe horizontal.

ZUSAMMENFASSUNG

Normale und labyrinthektomierte Katzen wurden fortgesetzten periodischen Coriolis Beschleunigungen unterworfen. Dieses ergab periodische Schwankungen im Umfang, eine Winkel-Verschiebung zwischen beiden Komponenten, eine winkelige Phase zwischen Coriolis-Beschleunigung und Reaktion, eine Beeinflussung der Geschwindigkeit der senkrechten Rotation auf die Reaktionsstärke und Umkehrungen der Richtung im Verhältnis zu den Umkehrungen der Coriolis-Beschleunigung.

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DISCUSSION

L. B. W. Jongkees: I would like to know the time constant of this recording apparatus.

M. Burgeat: Did you find as we did a diminution of the E.N.G. responses after repeated rotations?

L. B. W. Jongkees: I would like to know the time constant of this recording apparatus.

C. Fernandez (Reply): to Mr *Burgeat*: In our experiments it was found that repeating the rotation about the two axes was associated with rapid habituation. The frequency and amplitude of the periodic Coriolis *star* nystagmus diminished significantly after two or three runs as explained in the method of our work. For this reason the animals were tested at intervals of eight or more days.

to Mr *Jongkees*: All the recording was done with DC coupling.

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COMPUTER ANALYSIS OF ELECTRONYSTAGMOGRAPHIC DATA

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Electronystagmographic data obtained in the usual way by calorization are recorded on magnetic tape in analog form. The answers are then digitized and fed directly to a digital computer for analysis. The analog tapes have control pulses whereby it is possible to select separate data for any patient on the tape. The programs used now calculate frequency, amplitude, differentiated response and duration, etc., in order to evaluate the possible clinical use of the automatic procedure.

A system has been devised for converting nystagmograms or other experimental data, originally recorded on magnetic tape in analog form, to digital form with a variable sampling rate.

The system is flexible, so that it is possible not only to search for a particular recording on the tape but also to transfer any selected part of it to the computer. The transfer to the computer is entirely controlled by the user through certain control parameters to the reading programs. The construction of the electronic connection to the computer permits also the use of tape recorders which might cause interfering pulses on starting and stopping.

The system has been used for an automatic analysis of electronystagmograms recorded in the ENT-clinic, Sahlgrenska sjukhuset, Göteborg. It can, however, also be utilized for other types of analog recordings, e.g. mass spectra.

INTRODUCTION

In experimental research and clinical work a large amount of data is often collected which later on is to be treated and analysed. Typical examples are registrations of EEG and ECG and nystagmograms. For this purpose the computer has been put more and more to use. It is particularly desirable that the primary data can be made available to the computer without time-consuming manual operations. The actual measurements can first be recorded on magnetic tape in analog form and then analysed by the computer after sampling and conversion of the analog signals to series of digital numbers.



Fig. 1. Equipment for nyst gmu test

Such an input of analog data from magnetic tape has been carried out in various laboratories. In this paper a procedure will be described which represents a general and flexible system for different types of analog data. Thi is illu trated by a description of an automatic analysis of nystagmograms.

METHODS

1. Registration of nystagmus using Mi gograf d recording on magnetic tape
2. I terface of th magneti tape to the computer
3. Program system.

1. *Registration of Nystagmus*

The Mingograf 81 (D.C. Amplifier 8 channels recorder) (Fig. 1) is used for regi tering and transmitting the response from the patient to the magnetic tape recorder (Ampex SP 300 7 ch.) It i also used for record ing control pulses from a signal generat r producing a tone of 300 Hz fre-

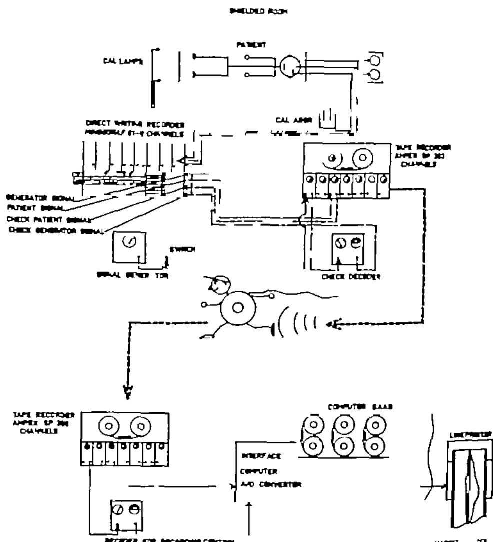
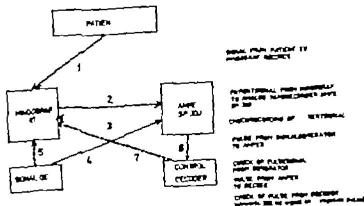


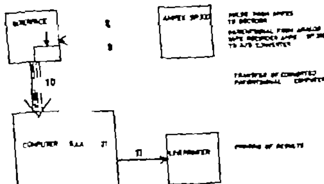
FIG 2. Recording and processing equipment for nystagmus test

quency (Fig 2) This tone is later decoded to a single pulse Every single nystagmus registration is then marked between two distinct pulses, a start and a stop pulse which determine where the computer analysis begins and stops All disturbing factors that are not of the same wave length and amplitude as the control signal are thereby eliminated In its present form the nystagmus test contains 9 different phases of measurement A block diagram of the procedure is given in Fig 3

Method of calibration for tape recording In order to get a uniform calibration of the signals from the patient with regard to duration and amplitude we have constructed a calibration unit that consists of a rotating contact disc which gives signals of 2 or 4 seconds duration for 30 seconds. The amplitude of the calibration is recorded so that a horizontal movement of the eyes of the patient with a deviation of 10 degrees gives a pulse of 10-mm height on the Mingograf curve

The advantage of this system of calibration is that it gives uniformity to computer analysis of different patient recordings





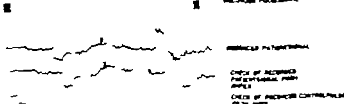


Fig. 3. Processi g of ystagmo test.

2 *Interface of the Magnetic Tape to the Computer*

The machine used is the Swedish Datasaab D21 computer (Fig. 4) It is a binary fixed-point single-address machine with 24-bit word (cycle time 4.8) using magnetic tape as backing mem ry This has been supplied with a fast input channel for analog information initially for use with an aut matic computer controlled film scanner (Abrahamsson, 1966)

A block diagram of the tape recorder interface to the computer is given in Fig 5 The signal from the analog tape (1) is amplified (2) and fed to the analog-digital converter (3) which gives 11 bits in 50 μs. Conversions are caused by pulses from the clock pulse generator (4) The latter has a ariabl frequency so that the sampling rate can be adjusted to suit the



FIG 4 Computer Datasaab D21

experimental conditions The clear command signal from the converter goes to the transfer control (5) which gives a signal to open the gate (6) if the two other input lines are set to open The transfer of the digital number in the converter output register to the computer core memory works on a cycle stealing basis and does not interfere with the program being obeyed by the computer

In order to control the input procedure program interrupts are obtained through a decoder (8) for each of the control signals recorded on a parallel channel on the tape These pulses change the state of the transfer control

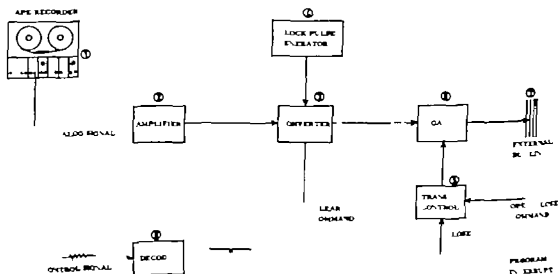


FIG. 5 I terf ce t comp ter

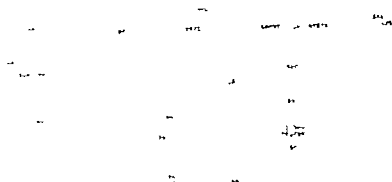


FIG. 4 Printout of y t gm lysis.

setting one input line to close No transfers to the computer are thus pos sible during a program interrupt The third input line to (5) is controlled by a special position in a computer register which is set by program This offers full program control over the data transfer

3 *Program System*

The following programs have been written for the analysis of nystagmographic data. The first two (READ and FILTER) are not specific for this particular application but can be used for any type of input data. They are written in a sembler language (Dac 1 autocode) whereas the analysis programs are coded in Algol.

A. *READ* The user specifies sampling rate, tape speed and the control signal program pplicable to the tape data The latter can ither be dif ferent f r the whole tape or be set to repeat itself in order to handle a number f similar experiments along the tape i.e series of patient data. It thu pos ible not only to search f r a particular recording on the tape but also t transfer any selected part of it to computer The transferred data are stored on computer magnetic tape for further treatment

B *FILTER* The nalog signal is often sampled at relatively high fre quency and then filtered numerically to give a smoothed ignal. The program allow the user to select a number of numerical filters for his problem. In addition the program accepts as input v rious descriptions of th digitized record, (e.g. patient data) All data are then stored on mag netic t pe in a form required by the D tasab Algol/Genius programming ystem.

C. *NYSTCOMP* This is the specific program fo analysis of nystagmus data recorded nd edited by th previous programs. It calculates

Fig 4 Computer Datasaab D21

experimental conditions. The clear command signal from the converter goes to the transfer control (5) which gives a signal to open the gate (6) if the two other input lines are set to open The transfer of the digital number in the converter output register to the computer core memory works on a cycle stealing basis and does not interfere with the program being obeyed by the computer

In order to control the input procedure program interrupts are obtained through a decoder (8) for each of the control signals recorded on a parallel channel on the tape These pulses change the state of the transfer control

Fig. 5 Interface to computer

Evaluation of the Computer Results

The computer results of different types of nystagmograms are being analysed to find adequate criteria for a useful clinical system About 200 nystagmograms on magnetic tape have been collected. We have used recordings from the routine clientele A few typical cases with various vestibular disturbances have been selected for detailed study We have found a good correspondence between the computer results and the direct reading from the mingograf curves in the conventional way These preliminary results indicate that the computer analysis will give more information concerning details in the nystagmus reactions than the conventional analysis. More definite conclusions, however can be drawn when a large amount of data has been analysed and treated statistically

DISCUSSION

There are certain methodological points of importance for the solution of the problem that we wish to emphasize

1 The control pulse gave considerable trouble before we arrived at the solution described This pulse is of great importance for administration of the input procedure. Our solution has made it possible to obtain a reliable operating system by excluding disturbing start and stop pulses.

2. Voluntary eye-movements of excessive amplitude, which are very common in the initial period after calorisation, can be excluded from analysis. Other solitary eye movements of large amplitude during the reaction can also be excluded by an idealisation of the curve using the computer Even very small spikes on the slow phase of the curve are of interest as they give a higher differential value than the average inclination of the curve We have chosen an amplitude of 3 degrees as minimum value.

3 In many cases it is necessary that the direction of nystagmus could be distinguished by the computer This problem has been solved in principle.

In the near future we intend to use this computer analysis for the study f vestibular function with other stimuli such as rotation and pendulating t t (Greiner) Preliminary experiment are in progress.

RÉSUMÉ

Des résultat lectronystagmographiques btenu par ex men caloriqu d rout n sont enregistrés de faço analogu sur bandes magnétiques, puis tran formés et analysés pa u computer digital. Les bandes so t marquées par impulses de contrôle f d pourou retrou er les résultat d un malad particulier Le programme actuel utilise la fréquence l' mplitude la réponse différenciée la durée et pour lser la possibilité d' tiliser routinièrement cett méthode at m t sée

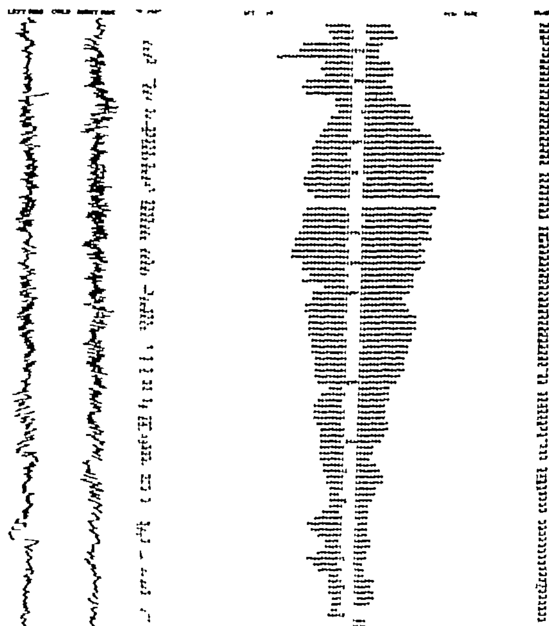


Fig. 7. Results of nystagmus analysis. Left: Direct recording. Right: Differentiated response.

(*a*) Differentiated response under correction for spontaneous nystagmus.
(*b*) Total amplitude
(*c*) Total number of beats within different phases of the recording
(*d*) Duration of each phase
(*e*) Occurrence in time of maximum response and its size
(*f*) Maximum frequency

D. *NYSTPRINT*. The response characteristics evaluated by NYSTCOMP are printed numerically. The differentiated response can also be displayed graphically on the line printer. Examples of the printout are given in Figs. 6 and 7.

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STROBOSCOPIC LAMINAGRAPHY OF THE LARYNX DURING PHONATION

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A significant advance in the use of radiological instruments for the study of human physiology was made in 1943, when Griesman reported that he used coronal laminagrams to observe the human vocal folds during phonation. He presented and discussed laminagrams made of several singers while they were producing various vocal pitches. Griesman's work showed that the laminagraphic approach was useful in the study of laryngeal phenomena. However, the first quantitative studies undertaken using conventional laminagraphy techniques were by Hollien & Curtis in 1934. In these studies, measurements of the cross-sectional area and thickness of the vocal folds were related to changes in fundamental frequency of phonation. Figure 1 is an example of a normal section laminagram showing the vocal folds during phonation. While laminagraphy represents an advance over older techniques of conventional radiological techniques, it suffers from several limitations. First, the image portrayed by this method is a composite built up during many vibratory cycles of the folds. The effect is one of blurring of the rapidly vibrating cord edges, which may be effected by such dynamic factors as amplitude of motion, duration of closed phase etc. Thus, while investigators can measure the composite image to derive cross-sectional area and thickness, enough differential variation may occur in the experimental procedure to cast doubt upon the validity of the result.

To overcome some of these obstacles and others which are related to such techniques as ultra-high-speed photography, a stroboscopic laminagraph has been developed which provides a series of laminagraphic X-ray photograph. The photographs display a coronal cross-section of the vocal folds at ten separate phases of the laryngeal cycle. The system has the advantage of allowing most subjects to be used, and requires no modification of the phonational mechanism such as the introduction of a laryngeal mirror or topical anesthesia.

The system still retains some of the limitations of conventional laminagraphy. That is, the resultant picture is still a composite image of numerous cycles, although the image is taken in the same phase. In addition, only one plane along the antero-posterior extent of the vocal folds can be visualized during any one experimental condition. The major advantage, however, is that one may obtain a coronal section of the vocal cords during a dynamic phonatory act.

ZUSAMMENFASSUNG

Elektronystagmographische Befunde welche auf übliche Weise durch kalorische Reizung erhalten wurden werden in Analogform auf Magnetband aufgenommen dann in Digitalwerten vorgewandelt und zur Analyse direkt in einen Digitalcomputer gegeben Auf dem Analogband befinden sich Kontrollsignale welche es erlauben die Sonderbefunde der einzelnen Patienten rasch zu finden. Unser Programm benutzt Frequenz, Amplitude Differentialanalyse Dauer usw mit dem Ziel, die mögliche klinische Auswertung des automatisierten Verfahrens abzugrenzen

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ENT Department University of Göt borg. Göt borg Sweden

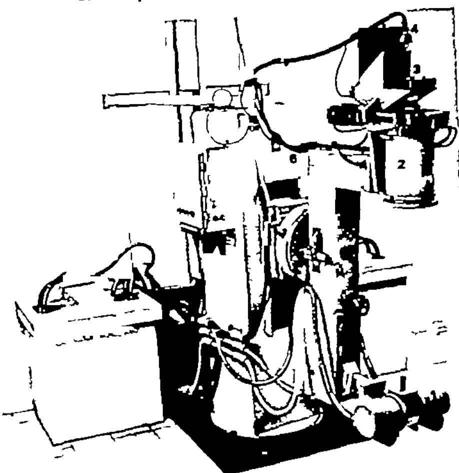


FIG. 2. The laminagraphic dri e, -ray and optical tem of STROL. The component pictured re (1) -ray tube (2) imag intensifier tube; (3) 35 mm camera; (4) TV camera (5) ke dri e, nd (6) yoke stand.

lowing th training periods, subject matched a t ne presented to them by earphon They and the experimenters monitored the vocal performance by a beat meter While the subjects did n t maintain a completely steady t n the variation around the mean f equency was somewhat less than − 2 Hz.

Th intensity of the ocal output was maintained by first asking subjects t produce the selected pitch at a comfortable level The microphone gain w then adjusted so th t if the subject dropped his int nsity by as much three dB, hi voice could not trigger the X-ray mechanism Excessive ocal output w m nitored by two person during each run, who disqualified a ubject on a particular run if he exceeded the intended level by three dB.

The resultant ten pictures n each experimental condition were examined



Fig 1 A photograph of a n rmal secti n l mi graph. P rtrayed re the ocal folds in coronal ross-secti n

Figure 2 is a photograph of the STROL mechanical system the accompanying legend identifies those individual components that can be seen externally It should be noted that this apparatus has been arranged specifically for photography with much of the associated equipment removed During actual operation the supporting components and a table for the subject are included Figure 3 provides the STROL schematics each of the components is identified on the diagram

The preliminary data reported here utilized four male subjects phonating at four separate fundamental frequencies of 98 124 155 and 196 Hz, which are four semitones apart and cover a full octave from G to G_1

The subjects vocal range was determined in a screening session by having them match complex tones on an ascending and a descending scale The total range of the subjects used was an average of 32 semitones. The widest range was 39 semitones while the most restricted was 27

The subject s were familiarized with the equipment and instructed in the procedure for the experimental session during a brief training period Fol

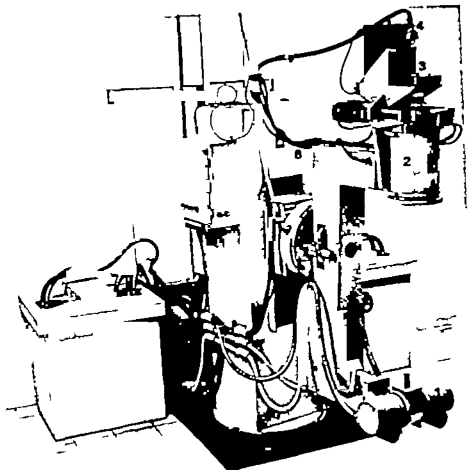


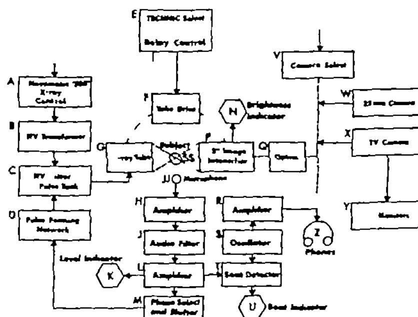
Fig. 2 The lamin graphic dri e, -ra and ptical yst m f STROL. The component pictured are 1) -ray t be (2) image intensifier t be; (3) 35 mm camera (4) TV camera (5) oke drive, nd (6) yoke st nd

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The resultant ten pictures on each experimental condition were examined

and the ones showing closure were subjected to cross sectional area and thickness measurements. The procedures for measuring the vocal fold pic tures were the same as those which Hollien & Curtis had employed earlier Figure 4 shows a highly stylized drawing of the way in which the folds were outlined for measurement The lines AB of the airway margins and



Fio 3 Block di gram f STROL.

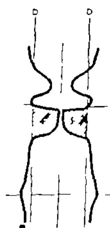


Fig. 4

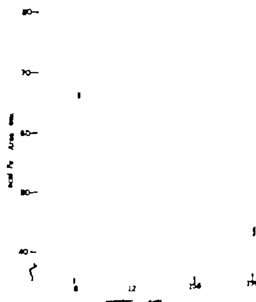


Fig 5

Fig. 4 A tra i g of a l m agraph f th ocal f ld h w g the ference li es sed in obtaining coronal cros secti n l are and th knes me surem t

Fig 5 Scatter pl t f cross- ect area mea ures b frequ es there re eight d t points at e ch of the frequencies

all other relevant lines were independently drawn on separate transparent sheets by two persons. In case of disagreement, redefinition by the two experimenters and measurements by a third judge were used. Through a long series of photographic trial and error the prints used for measurement were clear enough that disagreement among the experimenters was rare.

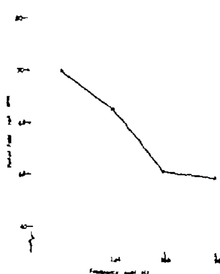


Fig. 6.

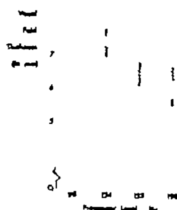


Fig. 7

Fig. 6. Mean of the area measurement for the four subjects.

Fig. 7. Variation in vocal fold thickness as a function of fundamental frequency.



Fig. 8. Mean of the vocal fold thickness measures.

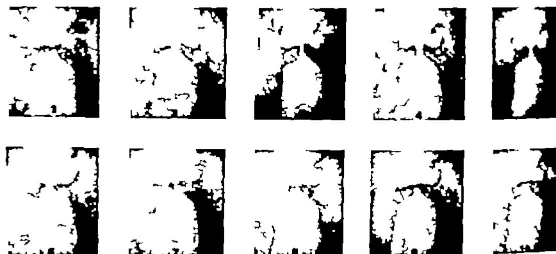


FIG. 0 An illustrati e series of troboscopic laminagrams sl owing the ibrat ry actio f the vocal folds in coronal cross-sectio

After the basic outlines of the folds were completed they were measured for cross sectional area by polar planimeter Planimeter measurements were made by two separate judges. The enlargement factor of the prints was determined and the planimeter measures were adjusted accordingly to give final measures in millimeters

The results of the cross sectional area measures are displayed in Figure 5. The eight data points at each frequency level represent area measures of the four subjects two vocal folds. While the wide range of area measurements for any one frequency level is apparent, the general trend is for vocal fold cross sectional area to be inversely related to increases in fundamental frequency

Figure 6 portrays an average of all four subjects area measurements at the four frequencies The apparent flattening out of the curve between the two highest frequency levels might be attributed to an artifact of the small group data, or that the subjects were phonating at a relatively high frequency probably at the upper end of their modal register

Figure 7 portrays changes in vocal fold thickness at the four frequency levels used You will note several more data points per frequency level than on the cross-sectional area measurements This is due to the fact that we added several subjects on whom we only had one or two frequency conditions A total of eight subjects data is shown with several re-test conditions included The purpose of adding the extra subjects is to indicate maximal differences among the subjects The trend is obvious that vocal fold thickness is inversely related to increases in frequency levels

Figure 8 is an average of these data, and illustrates the point again The present results, then, are presented as substantiating data for *Hollien & Curtis* previous conclusions using conventional laminagraphic techniques A much larger study is now under way which includes very precise control of frequency and intensity haracteristics. In the new study each subject

is required to produce frequency and intensity levels based on percentages of his own vocal ranges, rather than absolute levels used here. With more sophisticated techniques now employed, it is anticipated that the intra-subject variability may be reduced, and more closely related relationships defined.

It is not possible to provide motion pictures in a paper such as this one however Figure 9 is a set of ten stroboscopic laminagrams of a human subject These films are taken directly from our work prints and, by means of animation techniques, constitute the basis of our motion pictures. In these photographs, the subject is phonating at 124 Hz and at a relatively soft ocal intensity Even from photographs such as these it may be noted that only the superior medial borders of the vocal folds approximate closed time constitutes 20–30% of the duty cycle This finding is consistent with previously reported laryngeal photography data.

In summary stroboscopic laminagraphy i proving to be a useful research tool in the study of laryngeal function

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DISCUSSION

P H H linge W ppreciate Dr Coleman bringing this work to the Collegium and ask h m t tak our greetings to Dr Hollien and Dr Moore This important research tool add new dimension t the studies of phon tion which Dr Moore nd others has already made in thi field I should l ke t ask Dr Coleman if *other ph iologic fu ction f the larynx* such as cough a d deglutition, have been similarly studied. Also I hope h will tell us the approximate radiation e posure the laryn of the patient receives during such study

R F Coleman (Reply) t M *Holing* Thank you for your comments, Mr Holinger In reply t you first question I would review th f ct that STROL operates on a stroboscopic principle which in turn depend upon a relatively steady-stat ocal source In order t chieve series of phased pictures, we must use approximat l ten seconds of phonation from the subject. Since a cough or s llowing action is essentiall a transitory phenomenon, w are un ble to use STROL for such studies W *can of course* bserve su h function in real time without stroboscopic lamin graphy Concerning the rad ation e posure of the subject' larynx, I would say that this is quite variable due t different pulse rates, elated t the subject fundamental frequency Th ma imum exposure rates, how ever re well within conservati e limits set by the Radiation Co trol Committ of the U n versity of Florida.

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EINE FUNKTIONELLE STUDIE ÜBER DIE PNEUMATISATION DES SCHLÄFENBEINS

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Die enorm entwickelte Pneumatisation des Schläfenbeins bei den Pongiden insbes. beim Gorilla läßt eine spezifische Funktion vermuten wie sie bei den Walen bereits nachgewiesen wurde die Isolation des Innenohres gegen Knochenschall Modellversuche zeigen daß pneumatisches Gewebe eine schalldämpfende Wirkung erst oberhalb 1000 Hz entfaltet Eine mehrschichtige der Schädeldecke ähnliche Membran zeigt eine schalldämpfende Wirkung im unteren und oberen Frequenzbereich, aber eine ausgeprägte Eigenresonanz Die günstigste schalldämmende Wirkung ergibt die Koppelung der Membran mit pneumatischem Gewebe Die schalldämmende Wirkung erstreckt sich auf den ganzen Frequenzbereich mit Bevorzugung der oberen Frequenzen Die Eigenresonanz der Membran wird dabei deutlich gedämpft.

Ob die Pneumatisation des Schläfenbeins eine funktionelle Bedeutung hat und ob sie einer solchen Betrachtung wert ist, mag gewisse Zweifel erregen Solche Zweifel verstummen aber wenn man die Pneumatisation in ihrer fortgeschrittensten Entwicklung betrachtet

Die hochste Entwicklungsstufe erreicht die Pneumatisation des Schläfenbeines bei den Menschenaffen insbes. beim Gorilla Die eindrucksvollen Bilder die Sie im folgenden sehen und überhaupt die Anregungen zu unseren Untersuchungen verdanke ich dem Röntgenologen Professor Bergerhoff in Koln Die untersuchten Schadel stammen aus der von Professor Veit angelegten Sammlung des Anatomischen Institutes in Köln Für alle anatomischen und röntgenologischen Einzelheiten muß ich auf die ausführliche Arbeit die Herr Bergerhoff in Kürze veröffentlichen wird, verweisen.

Wenn man die ausgedehnte Pneumatisation des Felsenbeines des Gorillaschädels betrachtet, so kann man sich schwer dem zwingenden Eindruck entziehen daß hier der Pneumatisation eine besondere Aufgabe zugewiesen wurde Nach allen Richtungen hin ist das Innenohr durch eine mehrere Zentimeter dicke pneumatische Zellschicht von seiner Umgebung isoliert Diese Zellschichten treten nach lateral wie die Rontgenaufnahmen zeigen weit aus dem Schädel heraus, um die am Scheitel ansetzende mächtige Kaumuskulatur zu unterpolstern Das Schläfenbein selbst ist mit der Schädelbasis nicht knochern sondern nur bindegewebig verbunden Bei den übrigen Menschenaffen (Pongidae) dem Pongo (Orang Utan) Pan (Schimpanse) Hylobates (Gibbon) ist die Pneumatisation des Schlä



Abb. 1 Gorillaschädel, [illegible] terior-posteriore Aufnahm

Abb. 2. Gorillaschäd l, seitliche Aufnahme

f beins ähnlich strukturiert, wenn auch in wesentlich geringerem Ausmaße als beim Gorilla.

Bei allen diesen Art n befinden sich das Innenohr und die Paukenhöhle m Inneren eines ausgedehnten pneumatischen Zellsystems. Welches ist die Aufgabe dieses Zellmantel V n den gegebenen Möglichkeiten, die sich leicht ausschließen Schutz gegen mechanische akustische oder ther mische Einwirkung — erscheint die akustische Isolati n als die weitaus wichtigste

Eines der hervorragendsten Bauprinzipien des Gehörgangs ist die Herabsetzung des Knochenschalles. Die außerordentlich niedrige Schwelle für Luftschall kann überhaupt nur dann wirksam werden, w nn der Knochenschall t k gedämpft wird. Beim Kauen, Schlucken, bei der Stimmgebung beim Gehen usw entstehen mannigfache Körpergeräusche di als Knochen schall st renden und verdeckenden Charakter haben.

W e n h der Hörschwell diese Geräusche sind, läßt ich zeigen wenn die Knoch nleitung durch Verschluß des äußeren Gehörganges um ca. 10 Db rhoht w rd Békésy konnt unter diesen Bedingungen normale Gehbe wegu gen hören wie man sich leicht selbst überzeugen kann. Nach eigenen Beobachtungen läßt ich durch Verschluß des Gehörganges die Pulsation der Carotis interna w hrnehmen. Die Schwelle mancher körpereigener Geräusche liegt ffen ichtlich nur wenige Db unter d r n rmalen Hörschwell in Luftleitung.

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Die enorm entwickelte Pneumatisation des Schläfenbeins bei den Pongiden insbes beim Gorilla läßt eine spezifische Funktion vermuten wie sie bei den Walen bereits nachgewiesen wurde die Isolation des Innenohres gegen Knochenschall Modellversuche zeigen daß pneumatisches Gewebe eine schalldämpfende Wirkung erst oberhalb 1000 Hz entfaltet. Eine mehrschichtige der Schädeldecke ähnliche Membran zeigt eine *schalldämpfende Wirkung im unteren und oberen Frequenzbereich, aber* eine ausgeprägte Eigenresonanz Die günstigste schalldämmende Wirkung ergibt die Koppelung der Membran mit pneumatischem Gewebe Die schalldämmende Wirkung erstreckt sich auf den ganzen Frequenzbereich mit Bevorzugung der oberen Frequenzen Die Eigenresonanz der Membran wird dabei deutlich gedämpft

Ob die Pneumatisation des Schlafenbeins eine funktionelle Bedeutung hat und ob sie einer solchen Betrachtung wert ist mag gewisse Zweifel erregen Solche Zweifel verstummen aber wenn man die Pneumatisation in ihrer fortgeschrittensten Entwicklung betrachtet

Die hochste Entwicklungsstufe erreicht die Pneumatisation des Schläfenbeines bei den Menschenaffen insbes beim Gorilla. Die eindrucksvollen Bilder die Sie im folgenden sehen und überhaupt die Anregungen zu unseren Untersuchungen verdanke ich dem Rontgenologen Professor Bergerhoff in Köln Die untersuchten Schädel stammen aus der von Professor Veit angelegten Sammlung des Anatomischen Institutes in Koln Fur alle anatomischen und rontgenologischen Einzelheiten muß ich auf die ausführliche Arbeit die Herr Bergerhoff in Kürze veroffentlichen wird, verweisen

Wenn man die ausgedehnte Pneumatisation des Felsenbeines des Gorillaschädels betrachtet so kann man sich schwer dem zwingenden Eindruck entziehen daß hier der Pneumatisation eine besondere Aufgabe zugewiesen wurde Nach allen Richtungen hin ist das Innenohr durch eine mehrere Zentimeter dicke pneumatische Zellschicht von seiner Umgebung isoliert Diese Zellschichten treten nach lateral wie die Röntgenaufnahmen zeigen weit aus dem Schädel heraus, um die am Scheitel ansetzende mächtige Kaumuskulatur zu „unterpolstern" Das Schlafenbein selbst ist mit der Schädelbasis nicht knöchern, sondern nur bindegewebig verbunden Bei den übrigen Menschenaffen (Pongidae) dem Pongo (Orang Utan) Pan (Schimpanse) Hylobates (Gibbon) ist die Pneumatisation des Schlä



Abb. 1 Gorillaschädel, [illegible]terior-posteriore A[illegible]f[illegible]ahm[illegible]

Abb. 2. Gorillaschädel, [illegible]tliche A[illegible]fnahme

fenbeins ähnlich strukturiert, wenn auch in wesentlich geringerem Ausmaße als beim Gorilla.

Bei allen diesen Art[illegible]n befinden sich das Innenohr und die Paukenhöhle im Inneren eines ausg[illegible]dehnten pneumatischen Zellsystems. Welches ist die Aufg[illegible]be dieses Zellmantel[illegible] [illegible]n den gegebenen Möglichkeiten, die sich nicht an[illegible]schließen [illegible] Schutz gegen mechanische akustische oder thermische Einwirkung — erscheint die akustische Isolation als die weitaus wichtigst[illegible]

Eines der herv[illegible]rragend[illegible]ten Bauprinzipien des Gehörgangs ist die Herabsetzung des Knochenschalles. Die außerordentlich niedrige Schwelle für Luftschall kann überhaupt nur dann wirksam werden, wenn der Knochenschall stark gedämpft wird. Beim Kauen, Schlucken, bei der Stimmgebung, beim Gehen usw. entstehen mannigfache Körpergeräusche die als Knochenschall st[illegible]renden und [illegible]erdeckenden Charakter haben

W[illegible] nahe der H[illegible]rschwelle diese Geräusche sind, läßt sich zeigen, wenn die Knochenleitung durch Verschluß des äußeren Gehörganges um ca. 10 Db erhöht wird. Békésy konnte unter diesen Bedingungen normale Gehbewegungen h[illegible]ren, wie man sich leicht selbst überzeugen kann. Nach eigenen Beobachtungen läßt [illegible]ich durch Verschluß des Geh[illegible]rganges die Pulsation der Caroti[illegible] interna wahrn[illegible]hmen. Die Schwelle mancher körpereigener Geräusche liegt offen[illegible]ichtlich nur wenig Db unter der normalen Hörschwell[illegible] in Luftl[illegible]itung.

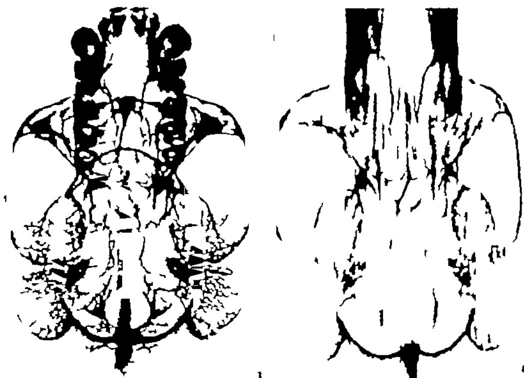


Abb. 3. Gorillaschädel, Basisaufnahme

Abb. 4. Gorillaschädel, Tomogramm horizontal 1:10 cm

Eine interessante Studie hat Békésy dem Prinzip des „minimalen Knochenschalls" gewidmet. Er schreibt: „Wenn man die beste Position für das Mittelohr im Schädel suchen will, so ist eine Lage so tief wie möglich im Schädel die beste, um den größten Schutz zu erhalten." Békésy zeigt, wie bei Biegungsschwingungen einer relativ dicken Knochenschale die äußere Hälfte gedehnt, die innere gepreßt wird, während in der Mitte zwischen beiden eine Indifferenzzone nur Scherkräften ausgesetzt ist. Infolgedessen ist bei Lebewesen mit dicken Schädelknochen (Mensch, Ochse) eine Lagerung des Mittelohres in der Mitte des Knochens zum Schutz gegen Knochenschall am günstigsten. Bei kleineren Tieren, deren Schädelwandungen zu dünn sind (Hunde, Katzen, Mäuse), tritt an die Stelle einer dicken Knochenschale der lufthaltige Hohlraum der Bulla, in den z. B. beim Meerschweinchen die Cochlea weit hineinragt. Es läßt sich allerdings einwenden, daß die anatomischen Verhältnisse beim Menschen wesentlich komplizierter als in dem von Békésy angegebenen Modell sind.

Es ist nun die Frage, welche Vorteile die Einbettung des Mittel- und Innenohres in pneumatisches Material gegenüber der in festen Knochen hat. Hierfür können folgende Gründe maßgebend sein: Das pneumatische Material ist im spezifischen Gewicht leichter. Da die lufthaltigen Zellen mit der Paukenhöhle in Verbindung stehen, dienen sie gleichzeitig als Luftraum hinter dem Trommelfell und gewährleisten die Beweglichkeit des Trommelfelles (Békésy 1960). Sie erleichtern aus dem gleichen Grunde

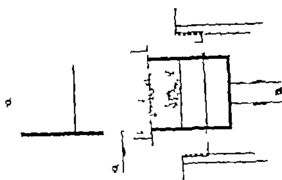


Abb. 5. Prüfgerät für akustische Widerstände

die Tubenfunktion. Letztlich hat poröses Material selbst schallabsorbierende Eigenschaften. Mit der letzteren Frage, in welchem Umfange auch pneumatischen Zellen diese Eigenschaft zukommt, haben wir uns experimentell etwas näher beschäftigt.

Für Messungen der akustischen Eigenschaften pneumatischen Gewebes standen zwei Wege zur Verfügung, die Untersuchungen am lebenden oder toten Schädel oder Modellversuche an künstlich nachgebildetem Material, d. h. an Blasenkunststoff. Die Möglichkeiten der ersteren Methode wurden von uns eingehend erwogen, da uns aus der Sammlung des Anatomischen Institutes der Universität Köln mehrere sehr gut präparierte Schädel großer Mensch affen, u. a. des Gorilla zur Verfügung standen. Es verstand sich aber von selbst, daß die wertvollen Sammlungsstücke auf keinen Fall beschädigt werden durften. So war es leider ausgeschlossen, etwa in die Paukenhöhle oder das Innenohr ein Mikrofon einzubauen. Da außerdem die akustischen Bedingungen infolge des anatomischen Baues des Felsenbeines sehr unübersichtliche sind, entschlossen wir uns zu Modellversuchen, bei denen die akustischen Verhältnisse einwandfrei übersehbar sind. Der Einwand, daß das Modellgewebe vom Körpergewebe allzu verschieden sei — ein Argument, das sehr häufig von Medizinern gegen Modellversuche vorgebracht wird — wiegt nicht allzu schwer. Es zeigt sich vielmehr, daß es mehr auf den strukturellen Aufbau des Gewebes als auf seine physikalisch-chemische Beschaffenheit ankommt.

Zur Messung des akustischen Widerstandes des offenporigen Blasenkunststoffes wurde ein Prüfgerät benutzt, das in Abb. 5 dargestellt ist. In der Versuchsanordnung befindet sich links der Ansatz für die Schallquelle, rechts ist das Meßmikrofon angebracht. In der Mitte kann poröser Kunst

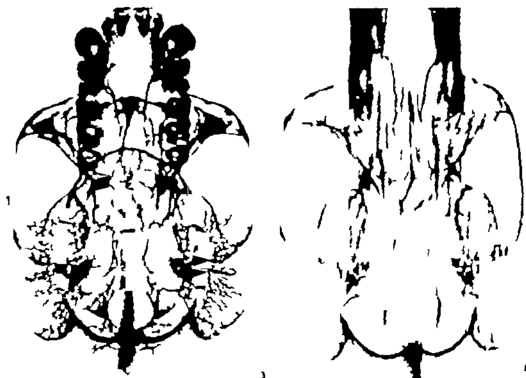


Abb. 3. Gorillaschädel. Basisaufnahme

Abb. 4. Gorillaschädel. Tomogramm horizontal 10 cm

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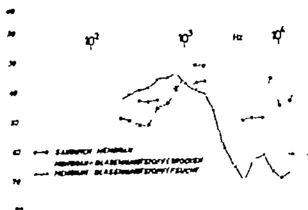


Abb. 7 Schalldämmung d rch Membra d poröser Kunststoff (T rsfilter)

50 Db. Die schalldämmende Wirkung ist, wenn die Substanz befeuchtet aber wieder ausgepreßt wird, so daß die Poren lufthaltig sind, kaum meßbar größer Sie ist deutlich größer wenn die Poren Wasser enthalten

Eine schalldämmende Wirkung auch bei tieferen Frequenzen (200–1000 Hz) wird erzielt, wenn dem porösen Kunststoff eine mehrschichtige Membran (Sandwich Membran) die in ihrer Dicke und Struktur etwa der Schädeldecke entspricht, vorgeschaltet wird. In diesem Falle beträgt die Schalldämpfung bei 200–1000 Hz 40–45 Db und steigt bis auf 60–70 Db bei 10 000 Hz. Die Eigenresonanz der Membran bei 1500 Hz (Schädel 1800 Hz) wird durch den porösen Kunststoff deutlich gedämpft (Abb 7)

Die Schalldämpfung im porösen Material kommt dadurch zustande daß die Luftteilchen in den Poren durch den einfallenden Schall zum Schwingen erregt werden und daß durch Reibung Schallenergie in Wärme verwandelt wird Die Schallabsorption poröser Stoffe ist stark frequenzabhängig und bei tiefen Frequenzen nur gering Zur Schallabsorption tiefer Frequenzen eignen sich Materialien, die zu Biegungsschwingungen fähig sind (Trendelenburg, 1950)

Schon frühere Untersucher haben sich mit der Frage des Schallschutzes durch das Luftraumsystem der Pneumatisation beschäftigt. Dabei wurde jedoch her n die Möglichkeit einer Innenohrschädigung gedacht. Wittmaack (1934) der di heut erla sene Theorie der Lärmschädigung durch Knochenleitung v rtrat, vermutete eine Verstärkung der Knochenleitung im pneumatisationsgehemmten Warzenfortsatz. Link & Handl (1955) haben in der Pneumatisation inen Schutz gegen Lärmschwerhörigkeit gesehen. Von dieser Auffassung unterscheidet sich unsere in einem wesentlichen Punkte Die akustische Isolierung des Innen und Mittelohres dient nach dem Prinzip des minimalen Knochenschalles der Aufgabe die Luftleitung gegen Verdeckung durch Knochenschall, und zwar besonders im Ni eau der Hörschwelle zu sichern. Die Pneumatisation könnte außerdem die Eigenresonanz des Schädel dämpfen („Entdröhnungseffekt)

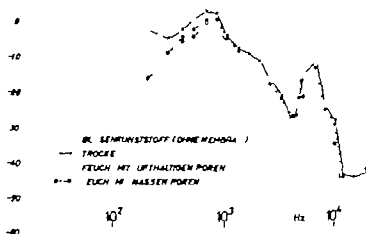


Abb. 6. Schalldämmung durch porösen Kunststoff (Terzfilter)

stoff mit oder ohne Membran eingeklebt werden. Ein akustischer Nebenschluß ist bei dieser Versuchsanordnung ausgeschlossen, da die Umwegdämmung stets größer als die Meßdämmung ist. Es wurden zwei verschiedene Kunststoffe mit folgenden Eigenschaften benutzt.

	N 2 mittel	N 10 mittel
Raumgewicht—Density kg/m	45–50	40–45
Zugfestigkeit—Tensile strength Kp/cm²	0,5	2,5
Bruchdehnung—Elongation of break %	90	210
Stauchhärte bei 40 (ohne Vorbehandlung) Load carrying capacity p/cm	97	219
Druckspannung—Compressive stress Stauchung, p/cm	9 0 81	8 0 210

Während das Raumgewicht, welches das Verhältnis der Poren zur festen Substanz wiedergibt, in beiden Fällen das gleiche ist, übertrifft der zweite Stoff hinsichtlich Zugfestigkeit, Bruchdehnung, Stauchhärte und Druckspannung den ersten bei weitem. Bei den Messungen ergab sich, wie vorweg bemerkt werden kann, zwischen beiden Stoffen kein Unterschied. Die zuletzt genannten Eigenschaften sind daher für die Schalldämmung ohne wesentlichen Einfluß. Inwieweit die Größe der Poren und das Raumgewicht von Bedeutung sind, soll noch eingehender untersucht werden. So könnte vielleicht die beim Menschen sehr variable Zellengröße, die nach außen auffällig zunimmt, von Bedeutung sein. Wie aus Abb. 6 hervorgeht, tritt eine schalldämmende Wirkung bei der von uns verwandten pneumatischen porösen Substanz erst ab 1000 Hz ein. Sie erreicht erst oberhalb 10 000 Hz

d'une fonction particulière Comme cela a été démontré hez la ba ln c est à-d re d' soler l'oreille lntern de la conduction osseuse Les recherches faites, à l' ide d n modèle ont montré qu le tissu pneumatique provoque effet d'amorti sement son re seulement au-dessus de 1000 Hz Ln membrane constituée de plusi urs couches semblables à celles du crân montre un ffet d amort sement da la one des fréquences basses et hautes. Mal vec une résonance nett l ffet d mortissement du son le plus f vorable est obtenu en couplant la membrane a ec du tissu pneumatique Il couvre un zon comportant toutes les fréquences a ec une préférence pour les fréquences éle ées. Aussi la résonan e de la membran est remarquablement réduite

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Bei den Walen finden sich in analoger Weise große, das Petrosum umgebende Räume die von Luftschaum erfüllt sind Diese Räume dienen, wie wohl heute allgemein als sicher angenommen wird der akustischen Isolierung gegen Knochenschall Wale verfügen über ein hochentwickeltes Gehörorgan mit der Fähigkeit zu binauraler Lokalisation Eine binaurale Lokalisation für Wasserschall setzt eine Isolierung der Felsenbeine gegen den Schädelknochen voraus Der enge Gehörgang der Wale leitet die Druckwelle des Wassers selektiv zum Trommelfell das wie der ganze schalleitende Apparat der Schallhärte des Wassers angepaßt ist (Fraser & Purves 1960 Reysenbach de Haan 1957) Auf diese höchst sinnreiche Weise wird der Wasserschall den gegeneinander isolierten Labyrinthen zugeführt und eine binaurale Lokalisation ermöglicht

Bei Landlebewesen deren Ohr Luftschall aufnimmt, ist die akustische Isolierung des Hörorgans gegen Knochenschall nicht in solchem Maße zwingend lebensnotwendig wie bei den im Wasser lebenden und Wasserschall aufnehmenden Cetacea Die Pneumatisation des Schläfenbeins entwickelt sich nur bei den auf höchster Entwicklungsstufe stehenden Primaten zur Vollkommenheit und ist beim Menschen bereits wieder in Rückbildung begriffen Nach der heute vorherrschenden Auffassung dürfte die Pneumatisation primär hereditär bedingt sein Ihre extreme Variabilität ist wie schon Darwin im Prinzip erkannte, ein sicheres Zeichen daß die Pneumatisation als Erbfaktor beim Menschen keiner Selektion mehr unterliegt und funktionell relativ bedeutungslos geworden ist

Mein herzlicher Dank gilt Professor Dr Bergerhoff Köln für die Anregungen zu diesen Untersuchungen und die Röntgenbilder Professor Dr Veit und Professor Dr Ortmann vom Anatomischen Institut der Universität Köln für die leihweise Überlassung der Schädelsammlung Meinen Mitarbeitern Professor Dr-Ing. Meister und Dipl Ing Ruhrberg für die ausgeführten Messungen

SUMMARY

The enormously developed temporal bone-pneumatisation of the pongides, especially of the gorilla has presumably a specific function as has already been proved with whales The isolation of the inner ear from bone-conduction Model experiments showed that the pneumatic tissue displays a sound-damping effect only above 1000 Hz A membrane consisting of several layers, similar to that of the skull, shows a sound-damping effect in the sphere of the medium and upper frequencies, but with pronounced resonance The most favourable sound-damping effect is achieved by coupling the membrane with pneumatic tissue It covers the complete sphere of all frequencies, with a preference for the upper frequencies. Thus the resonance of the membrane is remarkably reduced

RESUME

Le très important développement de la pneumatisation du temporal chez l'anthropoïde en particulier chez le gorille est probablement la conséquence

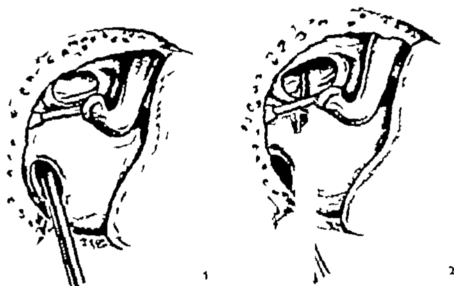


Fig. 1 Round window irradiation.

Fig. 2. Oval window irradiation.

The endoaural surgical approach to the ear windows is the same as for stapes surgery

A Round window irradiation

The round window is seen from an oblique angle and in very few cases its membrane can be seen. In some instances it could appear necessary to drill very gently the anterior border of the round window in order to obtain an easier introduction of the tip of the irradiator The middle ear cavity must be free of blood before applying the irradiator a drop of physiological solution is put on the round window niche to assure a good transduction of u s on the round window membrane

After 10–20 seconds a small "irritative nystagmus of 1 degree, directed toward the irradiated ear appears This nystagmus develops on two planes on the horizontal plane and on the rotatory plane sometimes vertical nystagmus is also present In some cases, after 60–90 seconds, the "irritative nystagmus" attenuates, and a paralytic nystagmus, directed toward the non-irradiated ear of the same entity of the first, appears. Sometimes we noticed that the two nystagmus are contemporaneous

The patient is discharged as early as 3 or 4 days after the intervention Fig 1

B Oval window irradiation

The irradiation presents two advantages

1 The oval window faces the vestibule and not the tympanic scale and the cochlear duct, which are facing the round window

Acta oto-laryngologica 65 221–233 (1968)

ULTRASONIC SELECTIVE IRRADIATION OF THE EAR WINDOWS AS A NEW TREATMENT OF VERTIGO AND TINNITUS

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The author presents the first results observed after ultrasonic irradiation at low intensity in a group of patients suffering from Menière's disease and other types of labyrinthosis (1) Round window irradiation seems to be indicated by cases of severe deafness accompanied by very troublesome tinnitus depending not only on Menière's disease but also on cochlear dropsical lesions, sudden deafness of vascular origin (2) Oval window irradiation seems to be indicated by Menière's disease in which hearing ought to be preserved

Kossoff (1966) has recently built a thin ultrasonic irradiator designed for irradiation of the round window He started from the ascertainment that when applied to the membrane of the round window the ultrasonic beam does not pass through bone and can therefore directly reach the membranous labyrinth with an intensity much lower than that one has to transmit to the ultrasonic beam when it is applied either on the lateral semicircular canal (Arslan's technique I) or on the bone vestibule (Arslan's technique II) As is known the bone wall of the labyrinth absorbs most of the intensity of the u s beam (only 10% of the intensity reaches the membranous labyrinth)

The Kossoff round window u.s generator of 3 5 Mh has an output which can be selected from 0 to 70 milliwatts, as states that an output of only 30 milliwatt is sufficient to abolish tinnitus and vertigo in patients with Menières disease In order to couple directly the u s beam to the tympanic scale facing the round window membrane the plane transducer of Kossoff's generator of 1 5 mm in diameter can be easily inserted in the round window The u s beam is irradiated only from one flat side of the probe top this side, placed in the round window niche is directed towards the vestibule on the assumption that the u s beam will be active there

METHOD

We applied this new irradiation technique proposed by Kossoff in 18 patients affected with Menière's disease or with other types of labyrinthoses We applied this irradiation technique to the oval window too



FIG. 1 Round window irradi tio

FIG. 2. Oval window irradiation

The endonural surgical approach to the ear windows is the same as for stapes surgery

A. *Round window irradiation*

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B. *Oval window irradiation*

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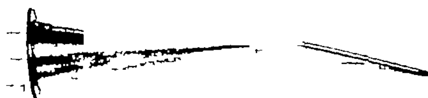


FIG. 3 Ultrasonic irradiation probe f r oval r round window

2 The position of the oval window is not oblique and therefore it is not necessary to limit the irradiation surface to only one side of the transducer

Incus and stapes are not luxated, neither are they damaged There is no difficulty with the presence of the stapes at the oval window as the end of the transducer having a diameter of only 1 5 mm can be easily inserted between the crura going on to the inferior part of the stapes and then applied on the platina inferior border and on the ligamentum anulare (Fig 2)

Ultrasonic Set

The irradiation of the middle ear windows is performed by applying a new probe from which a maximal output of 0 15 watt can be obtained The round probe (Fig 3) of 1 75 mm diameter is attached to a 12 cm long stainless steel holder which transduces ultrasounds

The holder is completely covered (with the exception of the tip, of 2 mm length) with a thin polyethylenic lamine in order to avoid side irradiation of the u s waves It can be easily introduced in the external ear canal and middle ear A drop of physiological saline solution is put in the niche of the irradiated window in order to realize a coupling between the tip of the probe and the irradiated membrane or platine

For round window irradiation it appeared sufficient to have an output varying between 0 025 and 0 060 watt

For oval window irradiation, where the u s must go partly through the bone of the platina we applied a little stronger output (varying, by single cases, between 0 08–0 1 watt)

As far as irradiation times are concerned we observed that in nearly all cases, nystagmus duration was—as an average value—of 3–5 minutes after this time it begins generally to decrease and reverse its direction (Fig 4)

RESULTS

The results are collected in Tables 1 and 2

No complications have been observed in any cases neither otitis media nor facial involvement

TABLE 1 *Response to the selective round window irradiation*

U.S. intensity 0.025–0.060 watt Irradiation time: 5'

(8 cases)

Hearing		Tinnitus		Dizziness	
Improved	0	Disappeared	5	Disappeared	5
Static	2	Decreased	2	Decreased	3
Impaired	3	Static	1	Static	—
Deafness	3	Increased	—	Increased	—

TABLE 2 *Response to selective oval window irradiation*

U.S. intensity 0.08–0.1 watt. Irradiation time: 3'–5'

(10 cases)

Hearing		Tinnitus		Dizziness	
Improved	3	Disappeared	5	Disappeared	9
Static	2	Decreased	4	Decreased	—
Impaired	3	Static	1	Static	1
Deafness	2	Increased	—	Increased	—

DISCUSSION

1. The possibility of reaching with the ultrasonic beam the membranous labyrinth, passing through the round and oval windows, present undoubtedly many theoretical advantages (*a*) a greater exactitude in dosing the intensity of the ultrasounds (*b*) the leakage of the u.s., which is so high when the irradiation goes through the labyrinth bone (90%) is reduced to negligible values (*c*) the great simplification of surgical procedure.

2. The anat mical features of the round window membrane are the following ( ) the round window membrane is placed obliquely and in front f the tympanic sc le and also of the cochlear duct (*b*) the round window hon nich i directed toward the cochlea (*c*) the distance between the r und wind w membrane nd Corti s organ is shorter than to the saccule (Anson 1919) (Figs. and 6)

Then, ven if the irradiator i inserted in the round window niche tow rd the est bul and its u.s. beam is irradiated from the posterior side f th probe tip, a the posterior bone wall of the niche is longer than the nter r m hobrak) the beam reaches inevit bly the perilymph of the t mp nic scala and i first directed toward the same axis of the cochlea Theref re m ing with drill a we did sometimes in our cases, the nter r border of the round window niche cann t change this direction of the u beam.

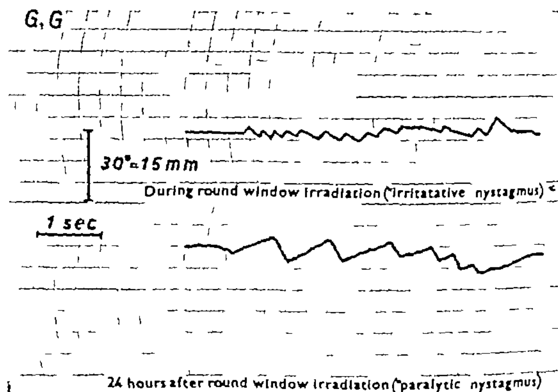


FIG. 4 Case 2 (G G) Electronystagmographic recording f nystagmus evoked during (bove) and after ultra onic irradiation of round window on the left side

3 Furthermore anatomical features of the round window allow formulation of a hypothesis aiming at interpreting the consequences of the irradiation of the round window

Disappearance of tinnitus, taking places much more rapidly and permanently than after irradiation by technique I and II and the impairment of the hearing (in some cases reversible) which can take place in some cases only 2 hours after the irradiation, evidence the hypothesis that *the convective endolymphatic currents first of all provoked by the u.s are running in the tympanic scala*

The endolymphatic current reaches the vestibular perilymphatic spaces only after having run through all the cochlear coils and the helicotrema and finally flows into the vestibule

Of course also small side u s waves may enter from the round window directly into the vestibule without making the tour of the cochlear coils, but the presence behind the round window of the terminal part of the cochlear duct and of the *ductus reuniens* and especially the anatomical direction of round window clearly facing the tympanic coil and directed towards the cochlea reduce the number of these diverging side waves. If we consider the very important fact that with the irradiation, by posterior approach of the semicircular canal or of the vestibule we obtain a great nystagmus, and that the perceptible hearing never becomes worse imme-

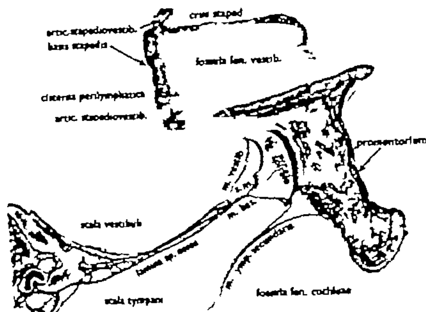


Fig. 5. Fossula fen cochlea round indow Fossul fen. estibuli ... l window s.m. = cochlea duct (After W. H. Bellucci & Eggston, *Microscopi Anatomy f th Temporal Bone* The Williams nd Wilki Co., Baltimore, 1957.)

diately (on the contrary in some cases, it improves even during the first days after the irradiation) and furthermore tinnitus never *totally* disappears by this peration, whereas the irradiation of the round window gives rise t exactly the opposite phenomena (remarkable cochlear changes, but mall estibular phenomena) all these facts support the hypothesis that the greater part of the u s. waves, arising in the tympanic scala, set out along the cochlear coils.

4 Irradiation f the oval window has two advantages (*a*) the anatomical position f the platina i not oblique but exactly facing the vestibule in which semicircular ampullae and otolithical organs are very near (*b*) cochlear structures are placed away from the irradiated area (Anson, 1949 M reover as the thickness of the platina is of a different value in it parts (Anson, 1949) ultrasounds are only partially reflected, and besides they go easily in the estibule through the ligamentum anulare

As pathological lesion by Menière disease are located in the saccule th irradiation of the oval window strikes the crucial point of the hydropical alterations.

A w observed in our patients, oval window irradi tion compared with round window irradiation, at the same u s. intensity provokes greater estibular phenomena and less cochlear phenomena even this fact seems to confirm the af rementioned hypothesi (see point 3)

Experiments carried out by Angell James *t al* (1961) and Arslan

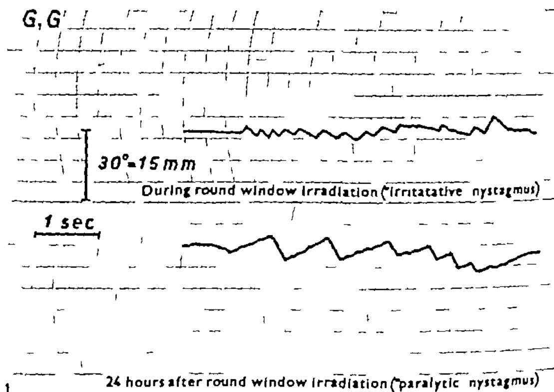


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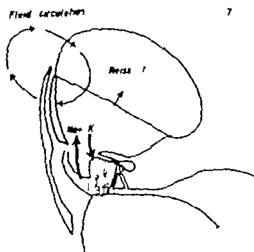


Fig. 7

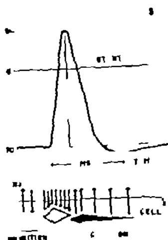


Fig. 8.

effect in the neuroepithelial cells, correspond to an hyperpolarisation, that i l say a functional pal y (with inhibitory effect?) of these cells. This fact is in agreement with the "paralytic nystagmus which appears during val window irradiation but we can't ctually state if this hyperpolarisation is connected only with a *direct* action of the u.s. waves on the neuro-epithelial cells, r even with some *cupular flexions* (for instance utriculo-fugal flexion of the lateral cupula) (Figs. and 8)

The "irritative nystagmus appearing during round window irradiation is by n mean in contradiction to what happens f r the oval window as we said, the round window is sufficiently far from the vestibular receptors t reduce the influence of the u.s. waves only for creating a convective endo-lymph tic current which enters the otolithic cavities th ough the route of the cochlear coil furthermore this current direction is not the same as th current coming from the oval window and consequently carries out other functional effects.

At present, lack of experimental knowledge compels us to look for an hypothesi interpreting the phen mena provoked by the irradiation of the round nd ov l windows, *only on the basis of th analysis of the functional nd clinical phenomena that we observe in our patients* This analysis, which i str mely rich in data to be evaluated, has been many times recom mended by u in order to interpret the effects of the irradiation, by posterior approach, of the semicircular canal (technique I) or of the vestibul (technique II)

In fact analysi of the characters of the different nystagmus arising *d ring* and *after* irra ll tion, con titutes, for the m ment the true para-meter which i valuable for an asses ment of the efficacy of the irradia-tion

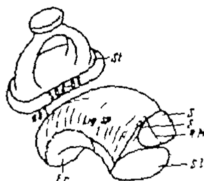


Fig 6 The distances between round window (f.r) *ligamentum spirale* and stapes (After C. Beck, *Hals Nasen Ohrenheilkunde* vols. III I G Thieme 1965.)

et al (1964 1966) have shown that the endolymphatic currents provoked by the u s are initially thermic currents They become convective currents and convey the ultrasonic waves, that, at the end, provoke the well-known cellular protoplasmatic lesions in the labyrinth neuro-epithelium. With regard to the phenomena that the ultrasounds certainly raise at the level of the labyrinth membranes and in the biochemical exchange between endolymph and perilymph, etc., we refer to the researches that Angell James *et al* (1961) Hughes & Chou (1964) Dum & Hawley (1965) carried out on the biophysical and biochemical effects that the ultrasounds produce in the organic tissues and membranes of the organism

It seems very probable, as stated by Hughes & Chou, that the u.s. act on the membranous labyrinth producing marked changes in the ionic balance between the cells and labyrinthine fluids and in the membranes permeability especially extruding $Na+$ and concentrating $K+$ in the neuroepithelium cells and/or in the *stria vascularis* Hughes & Chou have experimentally demonstrated the same phenomena in isolated muscle Such a disruption of the ionic balance could easily explain the cochleovestibular signs observed in our patients *during* irradiation of the round window (irritative nystagmus, rapid change of tinnitus)

Angell James *et al* studying the histological thermal and biochemical effects of the Bristol 3 Mh ultrasonic generator on guinea pigs and sheep, observed in the irradiated labyrinth (1) the perilymph "remained essentially normal in composition" (2) the endolymph showed an increased $Na+$ concentration and a decreased $K+$ concentration

The $Na+$ and $K+$ variations in the endolymph which have been found by Angell James *et al* (1964) correspond to the aforementioned hypothesis of Hughes & Chou endolymphatic increase of $Na+$ depends on extruded $Na+$ from the neuroepithelium cells and/or the *stria vascularis* whereas decrease of $K+$ depends from its cellular increasing Furthermore it must be assumed that the permeability of the Reissner's membrane may be altered too, after irradiation

The ionic changes which may occur hypothetically as an ultrasonic

8 A comparison between results obtained after r w irradiation and o.w irradiation allows at present the following clinical indications for irradia tion technique

(i) *round window irradiation seems to be indicated by cases of severe deafness accompanied by very troublesome tinnitus depending not only on Menière's di ease but also on cochlear dropsical lesions sudden deafness of vascular origin*

(ii) *oval window irradiation seems to be indicated by Menière s disease in which hearing ought to be preserved*

Further experimental researches and clinical observations in this field are nevertheless necessary

ACKNOWLEDGMENT

Our thanks are due t ou collaborators G. Molin ri, M.D and G. Babighian, M D for helpful cl nical observations of patients.

RÉSUMÉ

L auteur present les premiers résultat obtenus près irradiation ultrasonique ba se fréquenee sur un groupe de malades tteint de maladie de Menière et autres types de labyrinthose 1) L irradiation de la fenètre ronde parait être adiquee en cas de surdité grave sui le de bourdonnement correspondant à une pert n rosensorielle de l oui n e otosclerose avancée et 2) L'irradi tion d la fenetre ovale n'est indiquée que pour la maladie de Menière dans laquelle l'ouie loit être préservée

ZUSAMMENFASSUNG

Der Verf ser bringt di ersten Ergebnisse nach Ultraschallbeschallung mit niederer F t [illegible] die n l er Gruppe von n Morbu Menière und nderen Art on Labyri those l kenden P tienten erh lten wurden 1) Die Besch llu g des ru d n F ters sch int in Fällen von schweren Hörschädigungen, di zu gleich sehr beschwerendes T n I zeigen, angebracht, und zwar icht nur bei M rbu M er sondern uch be Presb cusis, traumatisch n Hörschädigungen von t gen neuroge en Horr rlusten f rtgeschrittener Otosklerose u w 2) Be sch ll g des len F nsters sche nt nur in den Fällen on M rbus Menière vor l [illegible] se n dene das Gehör erhalten bleiben soll.

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[illegible] J D ton, G. A., Fait [illegible], H. F B ller M. A., Wells, P N T [illegible], D A nd Com J 1961 [illegible] logical, thermal nd biochemical effect of [illegible] sound on the labyrinth and t mporal bon *Act Otolaryng* (Stockh) — 3-4, 306

TABLE 3 *Comparison between responses to selective irradiation of ear windows.*

	Round window	Oval window
Cochlear signs		
(a) During irradiation	Marked variations of tinnitus	No constant variations of tinnitus
(b) After irradiation	1 Improvement of hearing, but sometimes reversible impairement	1 Improvement of hearing
	2. Marked improvement of tinnitus	2. Improvement of tinnitus
Vestibular signs		
(a) During irradiation	1 Dizziness attack	1 Dizziness attack
	2. Horiz.-rotat. nystag. directed to the *irradiated* side	2 Horiz.-rotat. nystag with some vertical beats, directed to the *non-irradiated* side in 80 of cases
	3 At irradiation end inversion of ny direction	3. At irradiation end inversion of ny direction
(b) After irradiation	1 Vertigo for 3–4 hours	1 Vertigo for 1–2 days
	2. Transitory nystagmus	2. Transitory nystagmus
	3 Marked decrease of vertigo	3 Disappearance of vertigo
	4 Increase of vestibular reflectivity (caloric test)	4 No variations of vestibular reflectivity (caloric test)

6 The possibility of healing dropsical pathology of the labyrinth with a small u s energy *as our clinical results clearly demonstrate strengthens* the statement we formulated in our recent papers concerning u s application to surgery ultrasounds act not only with a destructive effect but with a correction of altered protoplasma belonging to the cellular target This corrective and selective effect is strictly proportional to the physical parameters of the u s., that is energy frequency output from generator irradiating surface (intensity) time of irradiation

However we were not wrong many years ago when we stated the possibility of healing Menière s disease with destruction of vestibular receptors, as has been proved by results of u s. irradiation with the high intensities given with the techniques I and II of Arslan but it must be now admitted that the same results can be obtained with a much smaller dose of u s

7 The functional and pathological signs which are evoked during and after ear windows irradiation are summarized in Table 3

ha been a recurrence f ttack after free interval of several years in some cases. It is doubtf l if th small d sage empl yed can produce any measurable hange in cell w ll permeability in isolated muscle cells in the light of Mr Hughes e periments. There must be a variable loss of transmi sion through the footplat depending upon thicknes and on gelation If accurate dosage i desired it would be necessary t remove the stapes, pply th *U.S* and replace the stapes in th win l w.

L. B W. J ngLee I am sorry that I don't feel very sure about the value of the result f any treatment of Menière disease as long a we ha e not both bjecti e method t assess th results and double blind statistical analysis of these results. Menière patient do strongly react to all kind f psy hological influences nd I am afraid that we are m v ng in the magical sph re

M Arsl (R ply) t M *Bordley* Th first patients were operated on two ears go f llowed over a period of two years, over 50% of them showed an mprovement of tinnitus. In some cases, result were spectacular s tinnitus d sappeared completely until recently

t Mr *H* *as* The main effect f irradiati n with ultrasound of th labyrinth organ is a selective cellula lesion the more differentiated and delicat are the cells (such as neuroepithelium) the more destructi are the lesions. When irradiation i performed with low intensity as for the ear windows, another ffect i achieved asodilat tion, cellular and ti sular increased metaboli ac ti it et Th val window irradi tion must not creat a fistula in the saccule on the contrary th plat na m st be n t dam ge l at ll

Theref re heari g ca be preserved s we bt ined in ne rly ll our cases.

t M *Angell James* (1) Ultrasoni frequency was 3 Mhz. (2) We did not perform Schlieren phot graphs. W used Gord n measurement method (3) Dosages were ery l w for w th output varied from 0.025 to 0.060 watt f r o w t wa from 0.008–0 1 w tt. But th ppearance of n stagmus a few seconds fter the irradiation begi wa the only sign of correct dosage a we al t kept fea from a too strong nyst gmus. Angell James i right, in that he believes that there a v riable los f transmission through the footplate de pending upon th knes for th reason we based the assessment of th dosage al upon th presence of yst gmus. (4) The proposal t remo stapes, apply ltra ou d and replace st pes, cannot be mad in Menière's patient a stapes detachment would be surely followed b deafness (the hydrop c saccule leans gainst the st pes)

t M *Jongk* There doubt that Menière s disease if t dent fication is based upon udiometric nd vestibular proof carried out with accuracy is n organic d sease Thi d sease belongs t those whi h are influenced (as, for stance cardio scular d seases) by psy hic factors and we would be very surprised t cardiologist would ff rm th t a discu ion concerning cardiac d seases is mo g n m gic l phere Every t log st experimented with the good nd d f n t result obt ned i Menière patient with correct medi al r (in few cases) w th urgical therap

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D pt f Ot hin laryngology th Universily f Padu Padua Italy

DISCUSSION

J E Bordley Mr Arslan s very interesting presentation showing his excellent results was very much enjoyed I am particularly interested in his unusually good results with tinnitus Did Mr Arslan follow these patients over a long period of time post-operatively? I raise this question because in some 200 patients where Mr Dandy performed a total section of the 8th nerve when these patients were followed over a long time less than 50% of them had relief of tinnitus.

W House (1) What is the principal of the irridiation (*a*) Destruction of the vestibular endorgan? (*b*) Creation of a fistula in the saccule? (2) What is the end point of the irradiation?

The original concept of ultrasonic irradiation was *selective* destruction of the vestibular organ and *sparing* of the cochlear function

Irradiation of the oval or round window with low dosage ultrasound would not seem capable of endorgan destruction Therefore the above questions.

J Angell James I congratulate Mr Arslan on his ingenuity and originality Would he please state what frequency is used Has he any photographs of the beam? How does he assess the dosage? Is his aim increased permeability or destruction?

Since the caloric responses are not abolished has he followed up *his cases* for a considerable period?

In our experience even when all caloric responses have been abolished there

has been a recurrence of ttacks after free interval of several years in some cases. It is doubtf l if th small dosage employed can produce ny measurable change I cell wall permeability in isolated muscle cell in the ligt t f M Hughes experiments. There must be a variable loss of transmission through th footplate depending upon thickness and on gelation If accurate dosage I desired it would be necessary to remove the stapes, apply the *U.S* and replace the stapes in the window

L. B W Jongkees I am sorry that I don't feel very sure about the value of the results f a y treatment of Menière disease as long w have not both objective methods to assess the result and double blind statistical an lysis f these results. Menière patients do strongly react to all kind f psychological influences and I am afraid that we are m ving in the magical sphere

M Arslan (Repl) to M *Bordley* The first patients were operated on tw ears ago followed er a period of two ears, o er 30% of them showed an impro ement of tin itus. In some cases, results were spectacular a tinnitus disappeared complet ly until recentl

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Therefore hearing can be preserved a w btained in nearly all our cases.

t Mr *Angell Jam s* (1) Ultrasonic frequency was 3 Mhz. (2) We did n t perform Schlieren photographs. W used Gord n easurement method. (3) Dosages were very low for r w the output varied from 0 025 to 0 060 watt for o. w t was from 0.008 – 0 1 watt But th appearance f nystagmus a f w seconds after th irradiation bega was the nly sign of a corre t dosage as we always kept lear from too strong n st gmus. Angell James is right in that he believes that ther I ariable loss of transmission through th footplat depending upon thi knes for th re son, we based th assessment of th dosage *nly* upon the presence of nystagmus. (4) The proposal to remove st pes, apply ultrasound and replace stapes, cannot be mad In M nière s patient t pes detachment would be surely f ll wed b) deaf ess (the hydropic saccule l an gainst the stapes)

to Mr *Jongkees* There i no doubt that Menière' disease if its identification is based upon audiometric and estibula proofs carried out with accuracy is an organic disease This disease belongs to those which are influenced (as, for instance cardiovascular diseases) by psychic factors and we would be very surprised if a cardiologist would affirm that discussion concerning cardi c diseases is "m ing in a magical sphere E ery ot logist xperim nted with th good and definit ve result obtained n Menière patient with correct medical or (in few cases) with surgical therapy

Acta oto-laryngologica 65 236–243 (1968)

NEW TECHNIQUES OF PLASTIC SURGERY TO REPAIR THE PHARYNGO-ESOPHAGEAL SEGMENTS USING CERVICO ACROMIAL FLAPS

A Previous Report

P M Barretto M.D
Saõ Paulo Brazil

The author describes several methods of utilizating the cervico-acromial flap (shoulder flap) be it to close pharyngeal fistulas in patients with heavy irradiated skin or to close large pharyngostomae fashioned after some pharyngo-laryngectomies These techniques have been used also in cases of cicatricial atresia of the pharynx and esophagus and in cases of esofagocoloplasties when the cephalic segment of the colon has been lost by necrosis Advantages (1) utilization of a flap from a not distant region with such a good blood supply that assures the vitality of the flap even when it has to be angulated or twisted to attain the area to which it should be applied (2) Possibility of using the bloody surface of the flap or the surface covered by the skin to fashion a tube for the reconstruction of the pharyngo-esophageal segment

During the XXth Brazilian Congress of Oto-Rhino-Laryngology held in Saõ Paulo in Sept 1966 the author presented, in collaboration with Almeida, a previous report on Plastic reconstruction of the pharyngo-esophageal segment with cervico-acromial flaps and will now present to members of the Collegium other techniques for repairing the pharyngo-esophageal segment, using the same kind of flaps

Cervico acromial pedicle flaps used for the first time by Mütter in 1842 in the treatment of a large retracting scar burn of the skin of the neck, have not been used, to the best of our knowledge by anybody else before us for the reconstructive surgery of the pharyngo-esophageal segment with the techniques we have been trying to standardize since 1960

These techniques, we hoped would be helpful for head and neck surgeons who are frequently confronted with cases of large pharyngostomae or fistulae of the pharynx, in patients with heavy irradiated skin which can only be closed by means of skin flaps brought from a distance

Another group of cases difficult to solve is that made up of serious retracting scars or cicatricial atresia of the pharyngo-esophageal segment due to the swallowing of caustic substances

Spina (1954) has emphasized the advantages of pedicle flaps for the repair of large retracting scars of the skin of the neck He has mentioned that these flaps, on account of their rich blood supply can be applied to

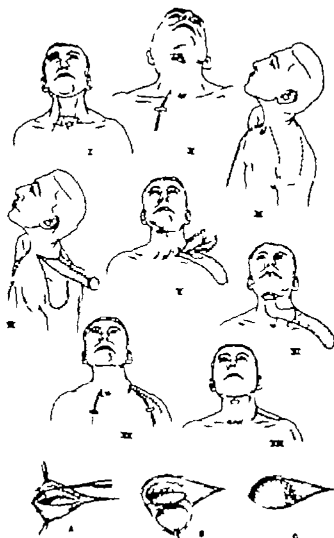


Fig. 1 Diagrams and detail f the thor techniques for the repair f the phary go-esophageal segment, using cervico-acromial pedi le flap I case 1 which phary go-laryngectomy with right neck dissection was done 20 day before Reconstructi sur-gery ha been done i three stages *1st stag* Di g. III; *2nd stage* Diag IV nd V det ils A B nd C. nd Diag. VII *3rd stage* Diag VIII Description page 240

areas with poor nutrition, and that they could help to transform the neigh boring fibrou tissue into younger connective tissue

In discussing the pathophysiological bases of the surgical treatment of scars from burns, Spina examined the factors held to be responsible for the retraction of th scars, the secondary retraction of the grafts and the reason for the differenc in behavior between graft and flaps. What he stated in relation to skin we ha e f und to be also true in relation to the digestive tract affected by the swallowing of caustic substances.



FIG. 2. Pictures taken du ing differe t tages to h w th large phary go toma the cervico acromi l flap is raised and utured at it iginal place in th first st ge (A B) Th tubul r flap h s be pa sed bel w th ki f nt l t al a pect of th neck and sutured t th base f the t ngu and p te l wall of th phary (C) The interrupted line hows wh re th pedi le flap ught t be cut t be utured t the esophagus (D) X-ra picture a d cl se-up f the p ti nt t h w fu cti nal nd co metic result (E F G)

First and second degree burns of the skin generally heal without leaving sequelae and their seriousness is related to the depth and extension of the burn and to the delay in epithelization Other factors stimulating the formation of fibrous tissue are the successive traumas on the granulation tissu of the wound

The same factors were previously pointed out by Bellinof & Charancoff (1935) regarding the acti n of caustic substances on the food passages. They constitute the pathophysiological bases for the treatment of the acute

and chronic corrosive esophagitis which have been stablished by Bellinof with his sequential papers published from 1930 up to 1942.

And these are the reasons why we are trying to take advantage of the pedicle flaps in the treatment of cicatricial atresia of the pharynx in cases of lye burns.

With regard to the treatment of pharyngeal fistulae which appear post operatively in laryngectomized patients previously submitted to intensive radiation therapy we have since 1960 with the collaboration of plastic surgeons been using cervico acromial flaps with great satisfaction.

Two cervical-acromial flaps may be prepared simultaneously or migration of the flap as far as the area to be covered may be obtained with one or two delays, without great discomfort to the patient

The rich blood supply of these flaps allow us not only to greatly surpass the ratio 1 1.5 between the width of the pedicle and the length of the flap, but also assures the vitality of the flap even when it has to be angulated or twisted to attain the area to which it should be applied.

The new techniques we are working on allow us to use the cervico-acromial flaps to fashion a tube for the reconstruction of the pharyngo esophageal segment. They have proven particularly advantageous because the raw surface of the pedicle is placed under the skin of the antero-lateral aspect of the neck, which gives very good cosmetic results.

This detail also prevents infection of the flap, which on account of a rich blood supply may act upon neighboring adult scar tissue helping it to change into younger connective tissue.

Another advantage is that the donor area can be easily closed by a simple approach to the edges of the skin or by free skin grafts, this being hardly noticeable afterwards.

The only inconvenience f our technique seems to be the delays necessary in the mobilization of the flap, which we have been carrying out according to the recommendations of the plastic surgeons.

The diagrams shown in Figs. 1 and 2 should give a better understanding of the techniques we are using to repair the pharyngo-esophageal segment

In Fig. 1 we have tried to show the different stages of the surgical treatment given to a patient with a cancer of the right pyriform sinus with a large xtension to the posterior wall of the pharynx.

We were obliged to perform a pharyngo-laryngectomy with a right radical neck dissection, but, knowing that we would have to resect an entire segment of the pharynx, we started the operation by raising the skin flaps so as to allow the plastic repair to be don later (Diag. I in Fig 1)

Through Diag. II and the picture reproduced in Fig 1 A we may estimate the condition of the patient when we started the reconstruction of the food passage

The plastic repair has been performed in three stages

First tage The cervico-acromial flaps wer raised and immediately sutured at their original place (Diag III)

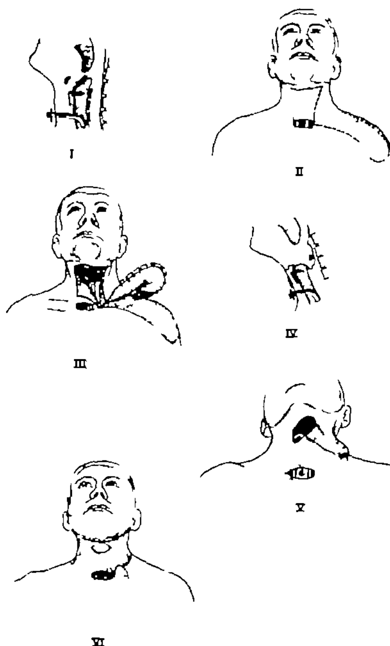


FIG. 3 Diagrams of the auth technique used in th repai f lr and food pa sages in case f cicatri ial atre i f th pharynx nd rvi l esophagu due to th swallowing of ly

Diag I Conditi n f th pati nt bef re th perati *D ag II* Th ski flap raised nd utured t th i riginal place (1st st p) *Di g III I\ nd * Different st ps of th 2nd stag i which ph ryngect my w s d n all sc tl w s rem ved and th tubula fl p tured t the phary x a d l rynx *Diag VI* Ill strates the 3rd stag in which the pha x wa losed and the tubular flap utured t segme t f the col brought up beh d th st rnum

Second stage (*a*) The pedicle flap was raised after a delay of 15 days, to fashion a skin tube

(*b*) The edges of the ph ryngostoma were freed (detail 4)

(*c*) A tunnel was made under the skin of the antero lateral aspect of the

neck, and the tubular pedicle flap turned to pass through it and be sutured at the base of the tongue and postero lateral walls of the pharynx (Diag IV V and VI, and details *B* and *C*)

(*d*) The skin of the anterior and lateral aspect of the neck was closed. A continued aspiration was applied into the tubular flap and a feeding tube passed through the esophagostoma (Diag VII)

Third stage After another delay of two weeks the lower segment of the flap was cut and moved to be sutured with the proximal extremity of the esophagus (Diag VIII and close-up picture in Fig. 2)

In the picture reproduced in Fig. 1 A one can also notice that we have fashioned the esophagostoma at the right side, trying not to interfere with the fashioning of the tubular flap

This last detail caused us, in our first case a little more difficulty at the third stage—a slight bending of the new pharyngo esophageal segment, which lately we saw could be avoided. However in spite of this, the cosmetic and functional results were very satisfactory as can be judged from other pictures also reproduced in Fig 2

Fig. 3 shows some diagrams to illustrate how we have used a cervico acromial tubular pedicle flap to treat a case of cicatricial atresia of the hypopharynx and cervical esophagus.

Even though we had already successfully used Ogura s technique in other cases, in this particular case we decided to use a tubular pedicle flap, in order to avoid secondary retractions which are always greater with free skin grafts.

The diagram reproduced in Fig. 3 will serve to illustrate the procedure performed in three stages, necessary to restablish the air and food passage

First Stage Skin flaps have been raised and immediately sutured in their original place (Diag II)

Second Stage After a delay of 1 days a pharyngectomy has been per f rmed and all the scar tissue involving the hiode bone the epiglothis, pharyngo-epiglothic folds and a segment of the posterior wall of the pharynx has been removed. *A tubular* skin flap was fashioned and its distal end sutured to the larynx and pharynx (Diag III IV and V)

Third Stage A segment of the colon was brought to be sutured to the skin tubular flap and the pharynx has been closed.

RESUME

L auteur présent diverses méthodes d'util sation d un lambeau cervico-acromial (lambeau d l'épaule) soit pour la fermeture pharyngo-œsophagienne, soit pou la reconstitution totale d segment pharyngo-œsophagien. Ces techniques ont et employées en ca de pharyngo-laryngectomies avec fistules ou large phary gostome d nécrose du segment céphalique du colon surface saign nte employé pou l'œsophagocoloplastie t en c d trésie icatricielle de l'œsophage et d l'hypophary x. Avantages 1 Utilisation d un lambeau facilement mobilisable vec de la peau glabre très résistant 2• pos ibilité d utiliser soit la sur face du lambeau, soit la urface converte par la peau.

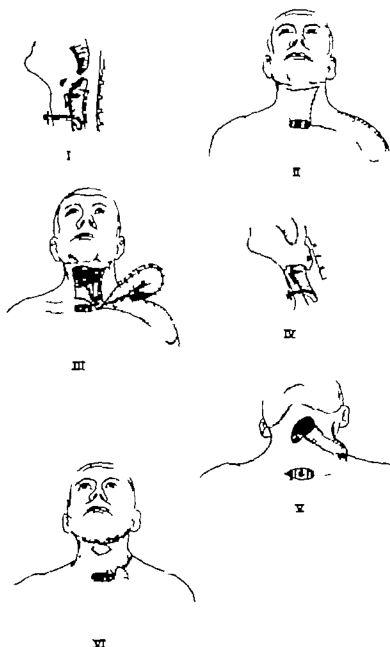


FIG. 3. Diagram of th author technique u ed in th repai f al and food passages in a case f cicatrici l atresia of th ph rynx nd cervical esophagu due t the swall wing f ly

Diag I Cond t of th pati nt bef re th pe t *D ag II* Th kin flaps raised nd s tured at th ir rigi al place (1st step) *D g III IV* d V D fferent st ps of the 2nd stag n wh l h a pharyngectomy wa d ne ll sc ti n w removed and the tubular fl p tured t the pharynx d larynx *D ag VI* Ill trates the 3rd st g in which the pha x w losed and th tubul fl p sutured t segm nt f the colon, brought up behind th t rnum.

Second stage (*a*) The pedicle flap was raised after a delay of 15 days, to fashion a skin tube

(*b*) The edges of the pharyngostoma were freed (detail *A*)

(*c*) A tunnel was made under the skin of the antero lateral aspect of the

material for such purposes nd that right colon (asce den) wa proposed t first, its mesenterial rtery and vein to be sutured to the corresponding neck essel (carotid external art., jugula vein) (Fairman Bristol & Mc N ll, Portsmouth) I London Prof Harrison and Ph Reading have pplied this method in a number f cases with good results. Recently J F Simpson f St. Mary's Hospital, London h s used in 3 cases the sigmoid colo transplantation in collaboration with Mr Eastcot, specialist in angiosurgery all cases healing successfully

P M Barrett (Reply) t M *Holinger* Th nking Mr Holinger s comm nts I should say that we only used irradi tion fter the m lignant degeneration of the papilloma

to M *Laskiewic* I also hav to thank Mr Laskiewicz for hi kind remarks nd should add that we have developed our present techniques after trying most of the other methods he has mentio ed W re really con inced that our techniques may bri g some contribution to th probl m.

ZUSAMMENFASSUNG

Der Verfasser beschreibt verschiedene Methoden zur Benutzung des zerviko-akromialen Lappens (Schulterlappens) sei es zum Verschluss von Pharyngostomien sei es zur kompletten Wiederherstellung des pharyngo-ösophagealen Abschnittes. Diese Methoden wurden benutzt bei Patienten die Pharyngolaryngostomien unterworfen wurden und in Fällen von Nekrose des zephalen Abschnittes des Kolonbogens der zur Ösophagokoloplastie benutzt wurde in Fällen von Narbenatresien des Ösophagus und der Hypopharynx Vorteile 1 Benutzung eines leicht mobilisierbaren Lappens mit glatter Haut die auch sehr widerstandsfähig ist 2 Möglichkeit die blutige Fläche des Lappens zu benutzen oder die mit Haut bedeckte Fläche

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DISCUSSION

P H Holinger We thank Mr Barretto for this interesting demonstration of the effective solution of a difficult problem May I ask Mr Barretto a question only indirectly related to his paper? Did the child who developed cancer in a papilloma of the larynx receive irradiation to the larynx and if so what was the interval of time between the irradiation and development of the cancer?

A Laskiewic Repair of the gape after laryngopharyngectomy has been one of the important problems ever since the first such operation wa performed in 1883 by Bernhard v Langenbeck The simplest method using two square angular flaps from both sides of the gape was devised by Gluck, Sorensen Hochenegg Marschik, v Eicken Henkels Sebileau Ormerod Ogura Ellis, M Lewis & Pietrantoni A rubber pharyngeal prosthesis of different sizes, surrounded by a Thiersch graft adapted to the upper end of oesophagus, was used by Sir Victor Negus in 1952 In 1953 Asherson J F Simpson & Seme used the anterior part of the larynx, with epiglottis as a covering flap to repair the gape after excision of the posterior part of the larynx in non-advanced cases of postericoid carcinoma. Then colon transplantation gained priority as the reasonable autoplastic

Guedry on the other hand, "assumes that the canals are at best insensi the linear accelerometers" He is of the opinion that although otoliths do not generate nystagmus impulses *per se* they can either modulate or main tain canal responses, under the influence of different acceleration condi- tions. Further it has been well known for decades that various kinesthetic organs can alter canal responses For a long time no data were known suggesting the otoliths as a possible etiologic factor for generating nystag- mic impulses until Jongkees & Philipszoon (1962) demonstrated nystagmic responses in rabbits in a lateral position and in humans looking to the extreme left or right. These responses were seen during the application of purely linear accelerations on a parallel swing—suggesting otolithic nystag mus probably on the basis of compensatory eye-movements and central corrections.

In our laboratory we also are confronted with a most intriguing problem of labyrinthology i.e which sub-organ is responsible for which eye-move- ments We conducted some experiments on rabbits in which a combination of two stimuli was applied to a pair of normal labyrinths—a constant rota tion about a horizontal axis together with a slow sinusoidal movement (.01 Hz) about a vertical axis. It seems a very simple matter but the mathematical evaluation of the generated spacial vector is as follows

$$\vec{a}_r(t) = \vec{\omega}\quad [\vec{\omega}\quad \vec{r}(t)] + 2\vec{\omega}_2(t)\quad [\vec{\omega}_1 \times \vec{r}(t)] + \frac{d\vec{\omega}_2(t)}{dt} + \vec{\omega}_2(t)\quad [\vec{\omega}_2(t) \times \vec{r}(t)]$$

a_r eventual ector
ω_1 angular locity of barbecue rotation,
ω_2 angular elocity of rotation bout ertical axis,
ector product,
distance bet een intersection axes and point of rotation (labyrinth),
t time

From the mathematical formula the xperts can read that the generated vector is the product of the centrifugal forces ev ked by the horizontal and the vertical axial rotation, the external product of the variation in velocity as a function f time of the vertical axial rotation, plus the coriolis term The moti e f choosing this seemingly extremely complicated stimulus was that it offers an easy method of measuring threshold values because the ector alters from zero to maximum and to zero again A second check i pos ible since the rotation about the vertical axis changes from clock w se t counter-clockwise inusoidally

Lastly th stimulu i three-dimensional, resulting in a stimulation of ll the cupula The resultant eye-responses were recorded with a type Elema A C amplifier with a time constant of about 10 Horizontal and v rtical lead were used for recording. The experiments were performed in the dark After the electrodes were securely placed intradermally the nim l were fastened in such a position that the lateral semi-circular can l were in a horizontal plane After this, the barbecue rotation and then the ertical axial rot tions were recorded separately the combined

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BARBECUE ROTATION IN COMBINATION WITH SINUSOIDAL ROTATION ABOUT A VERTICAL AXIS

A Preliminary Note

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The eye-movements caused by a combination of rotations about a cephalo-caudal horizontal axis and sinusoidally changing accelerations about a vertical axis were recorded A mathemetical analysis of the spatial vector is given The response is recorded by means of electro-nystagmography and analysed into an otolithic and a semicircular component It appears that not only the left and the right labyrinth, but also in one single labyrinth the otoliths and the semicircular canals are stimulated differently by the same vector

During the last few years rotation about a horizontal cephalo-caudal axis has caused much interest because the results obtained differed from the classic responses to rotation In the last case the axis of rotation was vertical The well known results and conclusions do not hold if the axis of rotation is horizontal Various authors, e g Guedry (1965) Correia & Guedry (1964) and Benson & Bodin (1966) conducted interesting experiments concerning the so-called barbecue rotation and tried to solve some of the problems which arose during it

What are these results? The salient features are to begin with, a nystagmus during constant rotation about a horizontal axis According to the classic conception there is no reason for this nystagmus to appear because of the absence of lymphokenesis Secondly the ningograph records an eye-deviation which alternates synchronously to the reorientation of the labyrinths to gravity At present we are not sure whether this is an otolith or a canal generated impulse These factors add to the problem of which sub-organ is responsible for the various eye-movements

Benson forwarded an attractive theory his so-called "Slosh" theory in which he explains that the configuration of the membranous canals would change according to its orientation to the linear acceleration or if the direction of gravity is changed in relation to the canals from a perpendicular direction *to a co-planar* direction that this could cause a change of the cupula-damping factor This modification of the endolymph hydrodynamics could explain some of the above mentioned phenomena

Guedry on the other hand, "assumes that the canals are at best insensitive linear accelerometers" He is of the opinion that although otoliths do not generate nystagmus impulses *per se* they can either modulate or maintain canal responses, under the influence of different acceleration conditions. Further it has been well known for decades that various kinesthetic organs can alter canal responses. For a long time no data were known suggesting the otoliths as a possible etiologic factor for generating nystagmic impulses until Jongkees & Philipszoon (1962) demonstrated nystagmic responses in rabbits in a lateral position and in humans looking to the extreme left or right. These responses were seen during the application of purely linear accelerations on a parallel swing—suggesting otolithic nystagmus probably on the basis of compensatory eye-movements and central corrections.

In our laboratory we also are confronted with a most intriguing problem of labyrinthology i.e which sub-organ is responsible for which eye-movements. We conducted some experiments on rabbits in which a combination of two stimuli was applied to a pair of normal labyrinths—a constant rotation about a horizontal axis together with a slow sinusoidal movement (01 Hz) about a vertical axis. It seems a very simple matter but the mathematical evaluation of the generated spacial vector is as follows

$$\vec{a}_r(t) = \vec{\omega}_1 \times [\vec{\omega} \quad \vec{r}(t)] + 2\vec{\omega}_r(t) \quad [\vec{\omega}_1 \quad \vec{r}(t)] + \frac{d\vec{\omega}_r(t)}{dt} + \vec{\omega}_r(t) \quad [\vec{\omega}_r(t) \quad \vec{r}(t)]$$

a_r resultual vector
ω angular velocity of barbecue rotation,
ω_1 angular velocity of rotation about vertical axis,
vector product
distance between intersection axes and point of rotation (labyrinth),
t time

From the mathematical formula the experts can read that the generated vector is the product of the centrifugal forces evoked by the horizontal and the vertical axial rotation, the external product of the variation in velocity as a function of time of the vertical axial rotation, plus the coriolis term. The motive for choosing this seemingly extremely complicated stimulus was that it offers an easy method of measuring threshold values because the vector alters from zero to maximum and to zero again. A second check is possible since the rotation about the vertical axis changes from clockwise to counter-clockwise sinusoidally.

Lastly the stimulus is three-dimensional, resulting in a stimulation of all the cupulae. The resultant eye-responses were recorded with a type Elema A.C. amplifier with a time constant of about 10. Horizontal and vertical lead were used for recording. The experiments were performed in the dark. After the electrodes were securely placed intradermally the animals were fastened in such a position that the lateral semi-circular canals were in a horizontal plane. After this, the barbecue rotation and then the vertical axial rotations were recorded separately, the combined

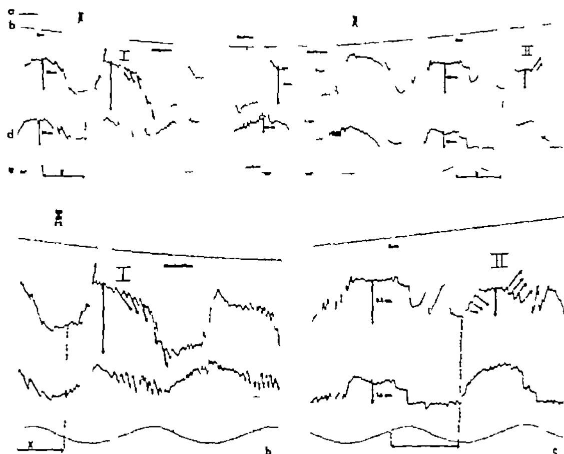


FIG. 1. Eye-movements of a rabbit during combined rotation about a horizontal and vertical axis. (a) Time in seconds. (b) Sinusoidal rotation (.01 Hz) about a vertical axis. (c) Movement of right eye. (d) Movements of left eye. (e) Barbecue rotation (i.e. about horizontal axis with constant speed). (a) Clockwise movement of (b). (b) and (c) Two responses taken from Fig. 1 c used by identical barbecue stimulus but opposite vertical axis acceleration. In I the vertical axis-acceleration is clockwise, in II counter-clockwise. The oblique arrows indicate the direction of the slow phase of the nystagmus, the vertical arrows the amplitude of the pendular eye movement.

stimulus of the barbecue and vertical axial rotation following. For the sake of clarity the recorded results are discussed with the aid of a few typical nystagmograms.

Here follow a few graphs to demonstrate our findings.

In Fig. 1 the acceleration about the vertical axis changes from clockwise to counter-clockwise. *This implies an inversion of the endolymphatic flow* and an opposite deflection of the cupulae. As one would expect, the nystagmus direction also inverts. What is interesting though is not that the nystagmus-direction inverts, but that the rhythm and phase of the eye-deviations stay constant and thus do not invert *pari passu* with the inversion of the endolymphatic flow and the resultant nystagmus. This can only be explained if one assumes that both eye-movements are generated by *different* sub-organs of the labyrinth, namely the canals and the otoliths respectively. The reason for the inversion of the nystagmus direction is

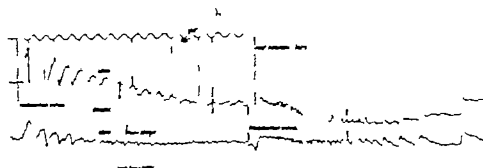


Fig. 2. Stopping the mov ment about the ertical l t the moment f maximum speed does not pro ok deviation of the erage ey position.

wholly in accordance with our classic conception of labyrinth physiology namely the inversion of the endolymphatic flow The explanation that the rhythmic pattern of the eye-deviations is not altered is that the ot oliths are stimulated by the alterati n and re-orientation to the direction of the gravity vector and is thu in phase to the barbecue rotation as indicated by the eye-deviati n. Th alteration of movements about the vertical axis does not influence the linear vector at all The proof that the centrifugal force evoked by the ertical axial rotation has no practical influence on the direc tion of the gravity vector is demonstrated in Fig. 2. When the vertical axial rotation is halted at the point of maximal linear stimulation (within 3 seconds, thus a period well below the 10 time constant of our AC amplifier and the iso-electric line can be regarded as accurate) no deviation from the iso-electric line takes place. During one cycle of the barbecue rota tion at maximum angular speed of the vertical axial rotation the direction of the nystagmus inverts two times during one cycle on account of the hanging corioli accelerations. If the vertical axial rotation alters from w to c.c.w the directi n of th nystagmus is inverted. One further notices that the phase f th eye-deviation does not invert. It explains two facts.

1 The d rection of the nystagmus is inverted because of the coriolis-f rce in ersion whi h is brought about by the change of the movement about the ertical xi from c.w to c.c.w or v.v

2. Th ye-deviation is not inverted since the coriolis force generated by th abo e-mentioned movement is too little to alter the directi n of the gra ity ector

Thi demonstrates that, although in thi case the cupula system responds t the corioli timulation, the eye position does not

Th conclu ion that can be drawn from the above discussion is that the different movements ar caused by two different sub-organs—the canals and otoliths.

Another point of interest is the amplitude of the eye-deviati n *per e*

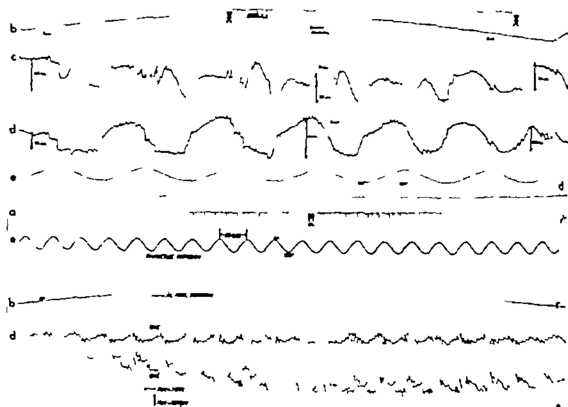


FIG. 3 The eye-movements prov ked by th same stimuli as in Fig 1 but for the direction of the rot ti n about th vertical axis wich is th counte -clockwise part of th inu (*d*) Speed 1 rot ti n/10 seconds. (*e*) Speed 1 rotati /2.5 seconds. See Fig 1

Regarding two comparable responses of the same eye at the same barbecue stimulus, *but with the difference that the vertical axial acceleration* has changed from c w to c c.w one notices that the amplitude of I is greater than that of II This is explained as follows In the case of I the direc tion of the slow phase of the nystagmus is co-directional with the eye-deviation and in the case of II the slow phase of the nystagmus is in the opposite direction to the eye-deviation It seems that the slow phase of the nystagmus increases the amplitude of the compensatory eye-deviation in one (case I) and reduces it in the other (case II)

This observation suggests two facts

(*a*) A further proof that two different components are generated by two different sub-organs. It would seem improbable for the cupulae to be thrust in one direction by the endolymphatic flow and yet at the same time be it by some other mechanism (Slosh) to generate an impulse in the opposite direction which would be responsible for the eye-deviation move-ment Concerning the canal influence on the eye-deviation it appears that the pure amplitude of the eye-deviation would be the average amplitude of the amplitudes of I and II which is 3 cm in the recording of the above case This corresponds to the value which we recorded for a barbecue rota

tion without concomitant rotation about a vertical axis at the same angular speed.

In Fig 3 the effect of a faster angular speed of the barbecue rotation is recorded. It appears that the amplitude of the eye-deviation is suppressed while the intensity of the slow phase of the nystagmus is increased, so much that it is hardly possible to distinguish the slow from the fast phase This also demonstrates the difference of the behaviour characteristics be tween the two different eye-movements. The nystagmic response is inten sely stimulated by the increased magnitude of the impulse but the eye deviation has become less intense Although this last phenomenon is not easily explained it suggests again that the two different eye movement are generated by two different sub-organs, both with their own characteristics.

CONCLUSIONS

From the above recordings and observations it seems that at least two different sub-organs must be responsible for the two different eye re sponses. It further appears that there exists a close coordination between these sub-organs. The amount of reciprocal influence depends on the com binati n f different accelerations, both rotatory and linear

RESUME

Les ouvements des yeux, provoqués par une rotation constante utour d un a h rizontal, céph lo-caudal combinée avec un accélération sinusoidal utour l un a e ertical ont été registrés pa électronystagmographie Une analyse mathém tique du ecteur spatial est *présentée. Les* courbes ont été nalysées. Elles montrent des élément t lithques et canaliculaires. L seul vecl *ur exerce* un stimulation d fférent sur le labyri the l droite et d gauch mais a sl sur la partie ot lithique et canaliculaire d'un seul labyrinth

ZUSAMMENFASSUNG

Di A genbewegu gen welche wahrend einer konstanten Drehung um eine ho izont le zephalo-kaudale Achse zusammen mit l er sinusformig wechselnden Beschleun gung um ine vertikale Achse entstehen werden elektronyst gmogra phisch registriert. Ei mathem tische Analyse des räumlichen Vektors wird gegeben D Kurven werden analysiert und zeigen Otolithen und Bogengangs Element l zeigt si h da beide labyrinthe sowie uch Otolithen und Bogen gange i es einzelnen Laby inthes om selben Vektor unglei h gereizt w rd n

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DISCUSSION

C Fernández We have also observed in our animals rotating about two axes the same modulation of the base line as shown by Mr Jongkees. All the recordings were done with DC coupling

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ABSORPTION AND TRANSFERRING OF THE COCHLEAR FLUIDS

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The perilymph is absorbed in the loose connective tissue of the modiolum, the endolymph is absorbed in the *planum limbi* nd the interstiti l l quid of the rgan of Corti in the inner spiral sulcus. The basin of the l of the queduct f the cochlea in a fetal phase transfers almost only perilymph. When fully developed many v ins of the bove-said basin are obliterated and the remaining ones transfer more blood than perilymph. From the interstitial spaces of the limbus the end lymph flows i to the capillaries towards the inner auditory vein and the interstitial liquid of the organ of Corti flows t wards th sam veins by means of short lymphatic vessels.

It is known, according to Siebenmann, that the loose connective tissue absorbs endolymph which is transferred towards the perinervous and subarachnoid spaces, while Kley holds it to be transferred by means of the ven us net. The cochlear endolymph is suggested to be absorbed by the endolymphatic sac (Guild, 1927) or by the outer spiral sulcus (Saxén, 1951) or by the limbus (Borghesan 10 0 1052, 1957) unknown is the existence of lymphatic vessels in the cochlea.

The persistent lack of ideas about these arguments has induced me to study from an hist logical point of view two human cochlea, one of a 6 m fetus and another of a *fetus at term I have chosen cochlea* in a phase of advanced development because, during this period, the cochlear fluids con tain a great quantity of albumen and of cellular detritus which leave traces of the *paths followed for the absorption*

In the 6 m fetus is clearly discernible the great amount of albumen in the cochlear fluids and, in the modiolum the large size of many vessels full of a gray substance with very few red globuli (Fig. 1) These vessels hav only endothelial tunics with scattered connectival cells they originate from mall vessels of the loose connecti e tissue of the modi lum (Fig. 2) nd run towards the vein of the aqueduct of the cochlea This connective tis ue I infiltrated by a gray substance and the cells of the very thin histiocytic net contain many black granuli the endothelial membrane lining the tis ue i constituted f cell with clear and swollen protoplasm (Fig. 3)

The cochlear fluid of the fetus at term are clear the loose connective tis ue of the modiolum i infiltrated by a *gray substance faced by a barrier* f macrophages (Fig 4) some of which are in the shape of clasmatocytes (Fig 5) The lining endothelium f the loose connective tissue as umes a

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DISCUSSION

C Fernándе We have also observed in our animals rotating about two axes the same modulation of the base line as shown by Mr Jongkees All the recordings were done with DC coupling

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ABSORPTION AND TRANSFERRING OF THE COCHLEAR FLUIDS

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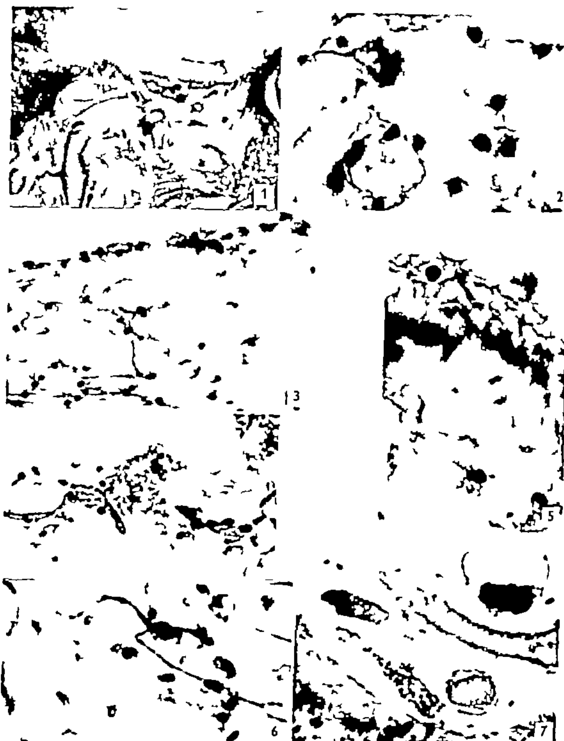
The perilymph is absorbed in the loose connective tissue of the modiolum, the endolymph is absorbed in the *planum limbi* and the interstitial liquid of the organ of Corti in the inner spiral sulcus. The basin of the vein of the aqueduct of the cochlea in a fetal phase transfers almost only perilymph. When fully developed, many veins of the above-said basin are obliterated and the remaining ones transfer more blood than perilymph. From the interstitial spaces of the limbus the endolymph flows into the capillaries towards the inner auditory veins and the interstitial liquid of the organ of Corti flows towards the same vein by means of short lymphatic vessels.

It is known, according to Siebenmann, that the *loose* connective tissue absorbs endolymph which is transferred towards the perinervous and subarachnoid spaces, while Kley holds it to be transferred by means of the venous net. The cochlear endolymph is suggested to be absorbed by the endolymphatic sac (Guild 1927) or by the outer spiral sulcus (Saxén, 1951) or by the limbus (Borghesan, 1950 1952, 1957) unknown is the existence of lymphatic vessels in the cochlea.

The persistent lack of ideas about these arguments has induced me to study from an histological point of view two human cochlea, one of a 6 m fetus and another of a fetus at term. I have chosen cochlea in a phase of advanced development because, during this period, the cochlear fluids contain a great quantity of albumen and of cellular detritus which leave traces of the paths followed for the absorption

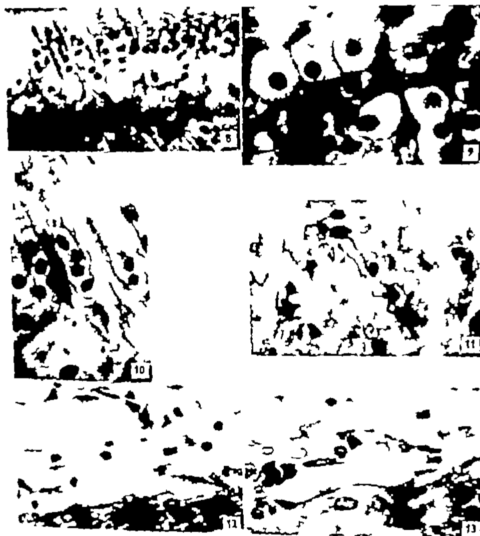
In the 6 m fetus is clearly discernible the great amount of albumen in the cochlear fluids and, in the modiolum, the large size of many vessels full of a *gray substance* with very few red globuli (Fig. 1) These vessels have only endothelial tunics with scattered connectival cells they originate from small vessels of the loose connective tissue of the modiolum (Fig. 2) and run towards the vein of the aqueduct of the cochlea. This connective tissue is infiltrated by a gray substance and the cells of the very thin histiocytic net contain many black granuli the endothelial membrane lining the tissue is constituted of cells with clear and swollen protoplasm (Fig 3)

The cochlear fluids of the fetus at term are clear the loose connective tissue of the modiolum is infiltrated by a gray substance faced by a barrier of macrophages (Fig. 4) *some of which are in the shape of clasmatocytes* (Fig. 5) The lining endothelium of the loose connective tissue assumes a

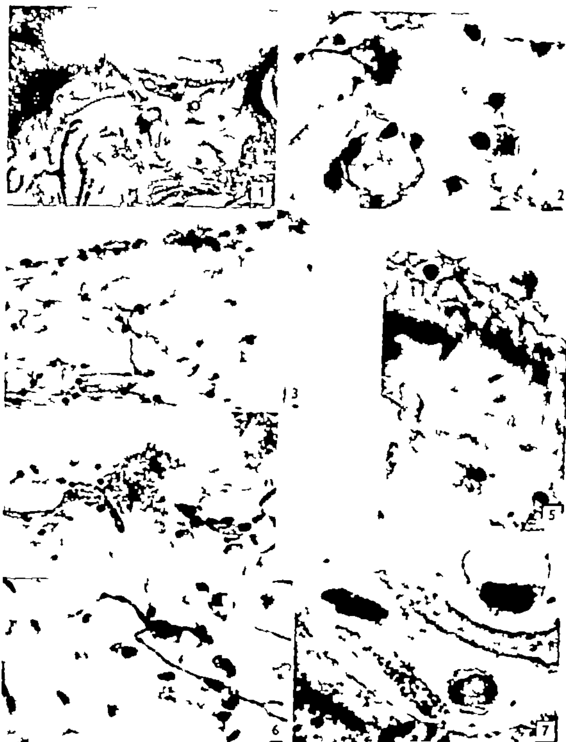


reticular aspect on count of the transparency of the cells constituting it and of the gray ubst ince infiltrating the intercellular spaces (Fig 6) The vessels of the modiol im which in the 6 m fetus contained gray substance here are empty or show few red globuli recent conguli, small parietal or obstructing thrombi in vari us phases of change while the connective tissue surrounding these vessels is in the first phase of sclerosis (Fig 7)

The limbus of the 6 m fetus is seen in an oblique section showing the



inner spiral ulcus, the interdental sulcus containing the epithelial cells and the connective tissue (Fig 8) Many interdental sulcus cross one another in various ways and re amply open in the endolymphatic subtectorial paces and in the inner spiral sulcus, while they are connected to the interstitial spaces of the connective tissue by means f anfractuous gapings Fig. 9) The cells of the interdental sulcu have globose nuclei, abundant protoplasm and constitute an epithelial f rmation that co rs and penetrates into th anterior face of the limbus the *planum limbi* (Fig. 10) which is lmost the *same as the planum emilunatum* The connective t sue of the limbus assumes an areolar aspect, since it is con tituted of many interstitial spaces of different width and shape (Fig. 11) some of them originate near the inner spiral sulcus and extend radially al ng the spiral lamina, quite close to the nervous fibres. These spaces begin as



reticular aspect on account of the transparency of the cells constituting it and of the gray substance infiltrating the intercellular spaces (Fig 6) The vessels of the modiolum which in the 6 m fetus contained gray substance here are empty or show few red globuli recent coaguli small parietal or obstructing thrombi in various phases of change while the connective tissue surrounding these vessels is in the first phase of sclerosis (Fig 7)

The limbus of the 6 m fetus is seen in an oblique section showing the

die Perilymphe resorbiert werden. Die Strukt r die Morph logi des Epithels nd des Bindegewebes des Limbus zeigen dass die cochleäre Endolymphe absorbiert wird

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lymphatic gaps more or less wide and with uncertain margins further on they are provided with a very thin endothelial tunic (Fig 12) conferring a vascular aspect but they contain no red globuli and join the veins of the modiolum (Fig 13)

The histological findings show that in the 6 m fetus the whole basin of the vein of the cochlear aqueduct acts as a great lymphatic way because it conveys a massive quantity of perilymph absorbed in the loose connective tissue of the modiolum It deals with a remarkable and transient phenomenon connected to the development of the cochlea, since in the fetus at term the veins full of perilymph are no longer traceable but the evidence that the above mentioned *phenomenon has taken place also in this last* fetus is offered by the reticular histiocytic reaction and by the vasal alterations causing obliteration These changes reduce the flow of the basin of the vein of the cochlear aqueduct and can signify that the perilymphatic balance in the phase of cochlear development is more active than later on

The remarkable structural likeness between interdental epithelium (*planum limbi*) and *planum semilunatum* suggests a similar function Voldrich thinks that the limbus *secretes endolymph* while in *my* opinion, many facts (morphology and structure of the limbus, existence in the cochlear duct of sufficient formations secreting endolymph, etc) force one to consider that the limbus is apt to absorb the endolymphatic fluids (endolymph and interstitial liquid of the organ of Corti) separately

From the interstitial spaces of the limbus the cochlear endolymph is transferred by hematic capillaries towards the inner auditory veins, while very likely *the interstitial liquid of the organ of Corti* at least in this phase of development seems to be transferred from the inner spiral sulcus towards the same venous system by means of lymphatic vessels.

I think I have new elements to confirm what I wrote in 1930 about the absorption of the cochlear fluids.

RÉSUMÉ

Par les recherches d aujourd'hui on peut tirer que les liquides cochléaires sont absorbés séparément la périlymphe par le tissu conjonctif de la columelle l endolymphe par le *planum limbi* et le liquide interstitiel de l organe de Corti par le sillon spiral interne Le bassin veineux de l aqueduc du limaçon dans une phase fœtale *contient seulement de la périlymphe après le développement de* la cochlée beaucoup de ces veines s oblitèrent et les restantes transferent plus de sang que de périlymphe L endolymphe est transférée par les capillaires qui arrivent au lacis des veines auditives internes et le liquide interstitiel de l organe de Corti est transféré par de brefs vaisseaux lymphatiques *qui se jettent dans les* venules de la columelle tributaires elles-mêmes des veines auditive internes.

ZUSAMMENFASSUNG

Die Makrophagen und die mit Plasma gefüllten Gefässe die im lockeren Bindegewebe des Modiolus enthalten sind zeigen dass hier die Zellzerfall massen und

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DURATION OF ANGULAR ACCELERATION AND OCULAR NYSTAGMUS FROM CAT AND MAN

II Responses from the Lateral Canals to Varied Stimulus Durations

F E. GUEDRY JR. and W E. COLLINS

From the U.S Naval Aerospace Medical Institute P nsacola Florida, and the Psychology Labora ry Civil Aeromedi al Institute FAA Oklahoma City Okla., U.S.A

A direct relationship between duration of acceleration and (a) declin f response duri g cceleration, (b) rate of decline of response after cceleration and (c) magnitud of secondary reaction is regarded as an indication f central process which limits a prolonged vestibula primary reaction The process is manifested by its influence on relatively bas c reflex react ns (nystagmus) in the cat and is more promi ently manifested in man by its influence n sensory perception.

INTRODUCTION

Ocular nystagmic responses elicited by angular acceleration have been found to be different in cat and in man (Collins & Guedry 1961) With prolonged stimuli (38 sec) a rise and decline of nystagmus during stimulation was obtained from cats for both lateral and vertical-canal stimulation. Human ubjects did not exhibit a comparable decline during prolonged stimulation Nystagmic reactions of the cat thus resembled the subjective (rather than the nystagmic) reactions of human subjects (Dodge 1923 Mittermaier & Romberg, 1956 Montandon & Fumeaux, 1957 Guedry & Ceran, 1959 Ek, Jongkees & Klijn, 1960)

At least part of the difference noted above in regard to primary nystagmic reaction appears related to the prominent secondary nystagmus which haracterizes responses of the cat to angular accelerations. Secondary nystagmu is pposite in direction to the primary response and it may reflect a process which develops during, and ppoies continuation of the primary reaction

The present investigation represents an extension of the earlier study (Collin & Guedry 1967) A rang of stimulus durations was used to larify relations between stimulus duration, the rate of decline of primary nystagmus, and the intensity of secondary nystagmus, and to compare further vestibular processes in cat and man.

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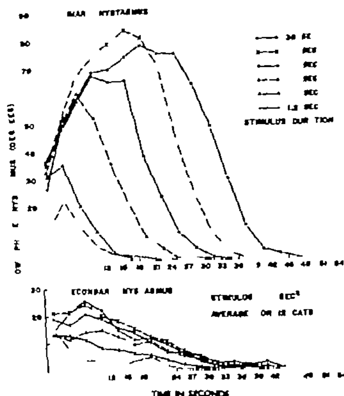


FIG. 1 Time-course plots of slow-phase ey di placement per 3-sec inter 1 for 12 cats posed t 6 stim lus duration of 4 /sec² ngular ccelerations. For the 21 nd 30 sec durations, responses reach peak and begi t decline duri g the stimul s. For the tw hortest durations, the peak response occurs after stimulus termination. Peak magnitud of the secondary reaction ppears related t stim l duration.

each stimulus (*a*) to the end of the primary response and (*b*) to the start of the secondary nystagmus. The number of beats of primary nystagmus which followed stimulus termination was tabulated.

TABLE 1 *Order of presentation of stimulu durations (in seconds)*

Duration ried from 1.2 to 30 sec. All angular acceleration were 4 /sec² nd rotation as al y counterclockwise Only the lateral canals were stimulated.

Human subjects	Cat	Trials 1	2	3	4	5	6
T & Ch	109 & 109	1.2	3.0	9 0	15.0	21 0	30.0
Dj & Do	110 & 111	3 0	9 0	15 0	21 0	30 0	1.2
Sa & Br	112 & 113	9 0	15 0	21.0	30.0	1.2	3.0
DA & Da	114 & 115	15 0	21 0	30 0	1.2	3 0	9 0
T & Fa	116 & 117	21.0	30.0	1.2	3 0	9.0	15.0
\ & Pa	118 & 119	30 0	1.2	3 0	9 0	15 0	21.0

METHODOLOGY

Cats

Apparatus

Rotational stimulation was provided in a light proof room with the Huffman Rotation Device (Collins & Huffman, 1964) Angular accelerations and decelerations were 4 /sec^2 separated by 54 sec of constant velocity Animals were tested in pairs (with their heads at the center of rotation) by means of a set of tiers (Collins & Updegraff 1966)

Restraint

Restraint was effected by the method of Henriksson Fernández & Kohut (1961) and in the manner described elsewhere (Collins & Guedry 1967)

Recording

An Offner Type R Dynograph recorded horizontal components of eye movements from needle electrodes inserted by the outer canthi A 3-sec time constant was used in amplification

Human Subjects

Apparatus

A Stille-Werner RS-3 rotator was programmed to provide accelerations and decelerations of 4 /sec^2 separated by 2 min of constant velocity

Recording

An Offner Type T polygraph (time constant 3 sec) recorded horizontal components of eye movements from surface electrodes taped by the outer canthi

Procedure

Each of 12 cats and 12 human subjects received 6 rotatory trials comprising 4 /sec^2 accelerations and decelerations for 1 2, 3 9 15 21 and 30 sec. Rotation was always counterclockwise and the order of presentation of the stimulus durations was counterbalanced among pairs of subjects as indicated in Table 1

None of the subjects had been used in previous vestibular experiments. Human subjects (6 men and 6 women) were instructed to signal onset and cessation of their rotatory experiences by means of a signal key

Scoring

Slow phase displacement of the eyes was scored by measuring the peak to base-line distance for each beat of nystagmus and summing these values for 3-sec intervals Time measurements were also made from the end of

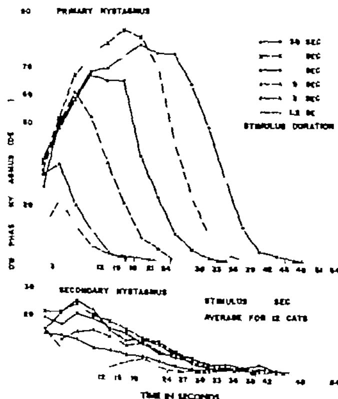


Fig. 1 Time-course plot f low-phase eye displacement per 3-sec interv l for 12 cats xposed to 6 st mulus durations f 4 /sec² ngula accelerations. For the 21 nd 30 sec durations, responses reach peak and begin t decline during the stimulus. For the two shortest durations, the peak response occurs after stimul termination. P ak magnitude of the secondary reactions ppears related to stimulus d ration.

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T BLE 1 *Order of presentation of stimulus durations (in seconds)*

Durations ried from 1.2 to 30 sec All gular acceleration were 4 sec² nd rot tion as lway counterclockwise Only the lateral canals were stimulated.

Human subject	Cats	Trials 1	2	3	4	5	6
Pr & Ch	108 & 109	1.2	3.0	9.0	15.0	21.0	30.0
Dy & De	110 & 111	3.0	9.0	15.0	21.0	30.0	1.2
Sa & Br	112 & 113	9.0	15.0	21.0	30.0	1.2	3.0
Dt & Da	114 & 115	15.0	21.0	30.0	1.2	3.0	9.0
T & De	116 & 117	21.0	30.0	1.2	3.0	9.0	15.0
Y & Pa	118 & 119	30.0	1.2	3.0	9.0	15.0	21.0

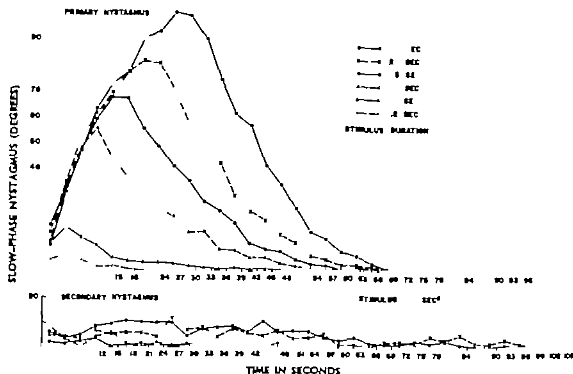


Fig 2. Time-course plots of slow phase eye displacement pe 3-sec int rval for 12 huma subjects exposed to 6 stimulu durations f 4 /sec² angular ccelerati ns. No decline f nystagmu during stimul tion i evident fo any duration (compare with Fig 1) Note that th peak resp ns for the three shortest duration occurs after stimulus termination. No secondary responses were vid nt for the 1.2 and 3-sec stimuli and n t all subjects showed secondary nyst gmus for the longer stimuli

RESULTS AND DISCUSSION

Cats

Measures of both response time and the number of beats of primary nystagmus following stimulus termination appear in Table 2 Post stimulus responses of greatest duration and magnitude occurred when stimulus durations were between 3 and 15 sec with the maximum post stimulus primary response occurring, in general with stimuli of 9 sec duration.

The slow phase velocity of primary and secondary nystagmic responses was plotted for each of the 6 stimulus durations (Fig 1) For the 21 and 30 sec stimuli there was a slight decline in response during constant angular acceleration Consistent with data from cats in the earlier experi ment (Collins & Guedry 1967) it appears that the nystagmic response reaches maximum intensity between 15 and 20 sec and declines after this, even though the stimulus is of constant magnitude and direction

The peak magnitude of secondary nystagmus appears directly related to the duration of the angular acceleration Secondary responses were obtained from all but one cat for the 6 stimulus-duration conditions the exception (cat 112) gave no secondary nystagmus following the 1 2 second stimulus.

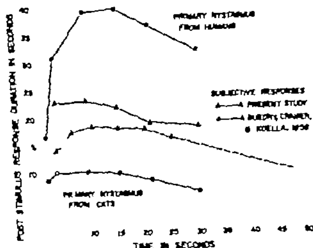


FIG. 3 Duration of the post-stimulus subjective and nystagmic reaction obtained in this study are compared with subjective data from an earlier study. The abscissa represents stimulus duration. Function depicted for the two sets of subjective data and for primary (slow-phase displacement) nystagmus from cats are in close agreement.

Human Subjects

Fig. 2 shows little or no decline in human nystagmus during constant angular acceleration irrespective of stimulus duration. This is consistent with human results of earlier studies (Collins & Guedry 1967, Collins & Guedry 1962, Guedry & Lauver 1961) but it is in contrast with results from cats in which nystagmus declined after about 20 sec of constant angular acceleration.

With brief stimuli (1.2 sec and 3 sec) it appears that in both man and cat the slow-phase velocity of nystagmus continues to increase ("overshoots") after the stimulus terminates (Figs. 1 and 2), whereas with prolonged stimuli, slow-phase velocity of nystagmus declines immediately after (in humans) or *before (in cats)* the stimulus terminates (Fig. 1).

As stimulus duration is increased up to about 15 seconds, the duration of the post-stimulus primary nystagmus increases. With longer stimuli, the duration of the post-stimulus primary response declines. In this respect human primary nystagmus corresponds *fairly well* in its temporal characteristics with the human subjective response. This is shown in Fig. 3 where the mean subjective turning scores from the present study are presented along with subjective data obtained in a previous study. In this earlier study (Guedry, Cramer & Koella, 1958) subjects had been trained in making subjective reports, whereas the present subjects had no preliminary practice. The rise and decline in duration of human nystagmus and subjective response as stimulus duration increases is also matched fairly

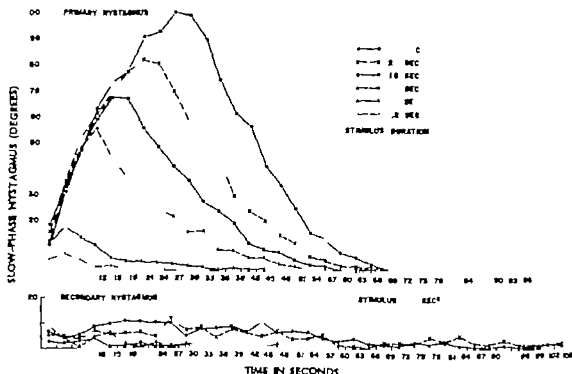


FIG. 2. Time-course plots of slow phase eye displacem nt per 3-sec int rv l for 12 huma subjects exposed to 6 stimulus duration of 4 /sec² ngular accelerati ns. N decline of nystagmu during stimulati n i vident for any duration (compare with Fig 1) Note that the peak response fo the three shortest durations occurs after stim lus terminati n No secondary responses were evident f r the 1.2 and 3-sec stimuli and n t all subjects showed secondary nystagmus for the l nge stimuli.

RESULTS AND DISCUSSION

Cats

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The peak magnitude of secondary nystagmus appears directly related to the duration of the angular acceleration Secondary responses were obtained from all but one cat for the 6 stimulus-duration conditions the exception (cat 112) gave no secondary nystagmus following the 1.2 second stimulus.

TABLE 3 *Measures of primary nystagmus following the termination of each rotatory stimulus for human subjects*

Each response value is mean of responses to acceleration and deceleration stimuli. Stimuli were 4°/sec² for 1.2, 3, 9, 15, 21, or 30 seconds.

Subject	1.2	3.0	9.0	15.0	21.0	30.0
Time from end of stimulus to end of primary nystagmus (sec)						
Pa	22.0	11.0	17.3	32.0	16.8	22.3
Da	12.8	25.2	42.4	34.1	61.6	45.3
Br	—	28.8	20.5	25.7	37.5	29.6
Do	18.3	19.6	38.9	51.3	38.3	39.8
Ch	13.1	25.1	40.0	33.0	24.5	23.9
Ro	13.8	41.3	28.4	34.9	44.2	40.5
V	10.9	62.2	44.0	41.3	58.4	37.9
T	—	20.9	42.8	26.7	33.1	27.2
Dt	31.8	42.0	44.4	48.4	40.1	35.7
Sa	21.3	22.3	53.6	44.1	32.8	26.8
Pz	7.3	28.1	57.9	40.3	39.2	28.5
Dy	17.8	46.8	42.4	45.6	33.7	27.2
M	16.9	31.2	39.5	38.8	36.8	32.4
Time from end of stimulus to start of secondary nystagmus (sec)						
Pa	—	—	—	—	—	26.1
Da	—	—	—	—	—	67.3
Br	—	—	—	—	—	—
Do	—	—	—	—	—	—
Ch	—	—	30.8	42.8	28.3	27.1
Ro	—	—	72.7	41.3	51.4	45.4
V	—	—	48.8	48.1	40.2	38.1
T	—	11.4	23.0	17.1	34.1	33.9
Dt	31.8	40.2	44.4	58.8	40.1	35.7
Sa	21.3	—	—	32.2	32.9	38.8
Pz	—	—	37.7	41.9	39.3	35.3
Dy	—	—	50.4	60.0	33.7	31.9
M	(*)	(*)	40.8	41.3	37.5	37.2
Beats of primary nystagmus after end of stimulus						
Pa	12.0	13.0	19.5	38.5	39.0	27.5
Da	10.0	25.0	88.5	82.5	94.0	81.0
Br	—	27.0	11.5	29.0	33.0	29.5
Do	9.0	12.0	39.5	47.0	42.5	39.0
Ch	7.5	29.5	47.0	43.5	42.8	37.0
Ro	8.5	24.5	43.0	50.5	70.0	62.5
V	4.5	30.0	41.0	41.0	37.0	32.5
T	—	23.0	53.0	46.0	51.5	38.5
Dt	12.0	39.5	65.5	42.5	40.5	55.5
Sa	20.0	31.5	78.5	73.0	52.5	54.0
Pz	4.0	12.0	34.5	34.0	29.5	34.0
Dy	15	20.5	47.0	81.0	46.5	43.5
M	10.4	24.6	41.7	50.2	49.7	43.7

* Too few scores on which to base means.

TABLE 2 *Measures of primary nystagmus following the termination of each rotatory stimulus for cats*

Each response value is a mean of response to an acceleration and a deceleration stimulus Stimuli were 4°/sec² for 1.2, 3, 9 15 21 or 30 seconds.

Cat	1.2	3.0	9.0	15.0	21.0	30.0
Time from end of stimulus to end of primary nystagmus (sec)						
108	10.9	12.4	14.6	10.6	8.1	6.0
109	5.9	8.3	8.2	5.4	4.0	1.6
110	18.5	7.3	9.2	12.0	5.0	2.3
111	7.1	11.1	8.8	6.5	4.3	.2
112	3.0	12.4	11.6	15.7	12.2	10.8
113	2.8	11.8	9.8	9.4	6.0	3.8
114	8.2	11.6	9.3	8.0	13.6	6.8
115	10.2	8.0	10.2	10.6	13.1	9.0
116	11.5	12.1	14.2	15.3	12.4	11.3
117	7.6	3.0	8.2	9.3	0.2	5.0
118	8.9	12.3	13.3	13.3	12.5	12.1
119	10.4	10.7	7.2	5.0	.2	2.5
M	8.8	10.1	10.4	10.1	8.7	0.5
Time from end of stimulus to start of secondary nystagmus (sec)						
108	15.6	15.4	20.8	15.0	14.5	13.2
109	7.0	16.9	13.5	9.9	6.5	0.2
110	15.9	6.6	12.9	6.0	9.4	6.7
111	15.0	10.8	12.6	10.8	7.5	10.6
112	—	14.6	17.5	24.4	20.1	18.1
113	15.7	18.3	14.1	11.6	9.0	7.5
114	12.5	12.7	14.7	25.4	15.1	15.6
115	17.3	19.5	14.6	16.7	15.0	14.0
116	13.0	10.9	21.3	17.5	15.4	16.1
117	11.2	18.0	14.8	12.6	13.0	15.6
118	9.3	16.3	15.3	15.5	10.4	15.7
119	15.2	14.9	11.8	11.4	9.5	1
M	13.6	15.6	15.3	14.5	12.6	12.2
Beats of primary nystagmus after end of stimulus						
108	4.0	12.0	10.0	12.5	11.5	0.5
109	1.5	7.0	9.0	6.5	2.5	1.0
110	3.0	3.0	6.5	6.5	4.0	3.0
111	2.5	7.0	8.5	7.0	4.0	0
112	2.5	8.0	11.0	18.5	10.5	9.5
113	2.0	7.5	9.5	9.0	5.0	3.0
114	5.5	8.5	12.0	7.5	17.0	5.5
115	4.5	7.0	8.5	9.5	16.5	10.5
116	5.5	8.0	16.0	18.0	9.5	18.5
117	4.0	5.0	—	8.5	3.0	12.0
118	12.0	13.5	17.0	19.5	19.0	15.0
119	4.0	8.0	5.5	4.5	0	1.5
M	4.1	8.0	11.4	10.6	0.8	7.3

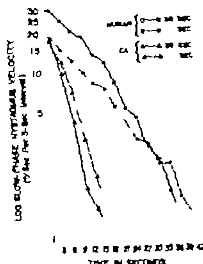


FIG. 4. Log plot of slow phase eye velocity following tw stimulus durations for cat nd human subjects. Data represent ystagmus me sured from the point of stimulus termination nd thus depict the rates of response decay. Decay i more rapid i cat and the longer stimulus d ration produces more rapid declines.

If it is assumed that secondary nystagmus reflects a process which develops during the primary reaction and opposes its continuation, then all of the differences between man and cat may be due to this secondary process in cat having a more direct control of nystagmus than does its c unterpart in man. The characteristics of subjective data reported by man resembled the alterations of nystagmus in cats during and after prolonged angular accelerations (Collins & Guedry 1967) and in some respects the nystagmus of man deviates from both the nystagmus of cat and the subjective responses I man during and after these unusual stimuli. It appears that the hypothesized secondary process exerts a control on man s sensory experience i.e the perceived angular velocity comparable to the control f nystagmus in the cat. This is not to say that the nystagmus of man is completely without the modulating influence of this secondary process because the rat of decline of both post-stimulus primary nystagmus and the occurrence of secondary nystagmus were influenced in man by the duration of the stimulus. However the control is apparently less consistent nd, hence probably less direct for the range of stimuli used in the present experiment. (Subsequent experiments have illustrated a pronounced se condary nystagmus in man when prolonged high-magnitude angular acceleration re used.)

It i parsimonious and reasonabl to assume that a single process account for (*a*) the decline in response during prolonged angular acceleration, (*b*) the increased response decline following prolonged acceleration,

well by the change in temporal characteristics of nystagmus in the cat, also shown in Fig 3 Reference to Tables 2 and 3 shows that, in both man and cat, time elapsed from stimulus termination to onset of secondary nystagmus increases and declines in a manner which approximately parallels duration of the primary reaction

Secondary nystagmus was not evident in the recordings of any of the human subjects for the 1.2 and 3 sec stimuli, and several subjects gave no secondary response to the 30 sec stimulus However frequency of occurrence of secondary nystagmus increased with stimulus duration and this may be interpreted as evidence for a relationship between stimulus duration and intensity of secondary response in humans similar to but more variable than that observed in the cat In comparison with secondary nystagmus of the cat the secondary nystagmus in man has a later onset lower average intensity (relative to man s primary reaction) and seems to be more subject to individual differences.

Tables 2 and 3 suggest that the number of beats of secondary nystagmus is more closely related to the duration of primary post stimulus nystagmus than to the duration of the stimulus This is in contrast to the maximum slow phase velocity of secondary nystagmus which seems related to the stimulus duration at least in the cat (see Fig 1) The decline in number of secondary beats with stimuli longer than 15 sec may signify an encroachment of the secondary reaction on the primary reaction

Primary nystagmus in the cat is shorter in duration and has a lower beat frequency than that of man for the range of stimuli investigated There is also a pronounced difference between man and cat in regard to the intensity ratio of secondary to primary nystagmus, the ratio being higher for the cat

A log plot of nystagmus slow phase velocity with respect to time also shows the cat to have a substantially different rate of decline of nystagmus (lower time constant) than man for comparable stimuli (see Fig 4) It also appears that slope of nystagmus decline for both man and cat changes as a function of stimulus duration the longer stimuli producing post stimulus nystagmus with a higher rate of decay (lower time constant)

General Discussion

Because neurophysiological data from cats are sometimes applied to the explanation of reactions in man it is important to compare the same response variables in men and cats exposed to identical vestibular stimuli Nystagmus in cats declined during prolonged constant angular acceleration in spite of efforts to maintain alertness, whereas nystagmus in alert men did not decline during prolonged angular acceleration the rate of decline of primary vestibular nystagmus following each stimulus was greater in cats than in man the ratio of secondary to primary nystagmus was higher in cat than in man

The conditions under which the "secondary processes" have been demonstrated, viz., prolonged constant angular acceleration, are seldom, if ever encountered in natural movement. Even a single, brief unidirectional angular acceleration followed by constant velocity does not occur in natural movement and, as noted in the present study intensity of nystagmus continues to increase briefly beyond the termination of short unidirectional stimuli. In natural movement, any brief angular acceleration is immediately followed by angular acceleration of opposite sign which returns the cupula toward its position of static equilibrium. Hence, in the case of either brief unidirectional stimuli or prolonged unidirectional stimuli, the vestibular reactions fail to follow the theoretical (Groen, 1960) cupula deflection. However this does not necessarily signify either an inadequate response system within the range of natural movements or a gross error in theoretical cupula mechanics. The departures from expected results signify a range of unnatural stimuli which are not accurately followed due to either inaccurate sensory detection or unfaithful central following of the input or both. Because the natural periods of movements of various animals are different (Melvill Jones & Spells, 1963) it is quite possible that the ranges of accurate sensory representation of movement, due to central and peripheral differences, will differ slightly in different animals.

The functional significance of the secondary process is not established. Some pathological conditions undoubtedly yield a central imbalance of spontaneous input from the two ears, and the "secondary process" may serve to readjust the point of homeostatic balance. Some complex motions of the head and body may terminate with minor residual cupula deflections, and this could require minor shifts in the point of balance between the two ears, which would be accomplished too slowly by the elasticity of the *cupula*. Tolerance to an increased level of vestibular stimulation encountered in land, sea and air travel may require a suppression at some level of vestibular inflow and it is possible that this secondary process serves this function. It has been shown that standard test stimuli administered after an angular acceleration are influenced in proportion to the duration of the preceding angular acceleration (Guedry, Cramer & Koella, 1958) and it may be assumed that this finding is another manifestation of the "secondary process". Moreover with repetitive angular accelerations, the peaks of both primary and secondary nystagmus in cats diminish and shift toward earlier occurrences (Collins, 1964; Collins & Guedry 1967). This suggests that the secondary process encroaches more and more upon the primary reaction and thus limits the magnitude and duration of the primary reaction with repetitive stimulation. In humans, there are large individual differences in secondary nystagmus. If the secondary reaction is a manifestation of an adaptive process which serves to limit the primary reaction, it may prove to be an indicator among people with comparable histories of motion exposure of individual differences in ability to habituate to repetitive vestibular stimulation.

and (c) the increased secondary response following prolonged acceleration. The possibility that the cupula endolymph system is under-critically damped, contrary to the common supposition would explain a secondary response but this seems at variance with much of the evidence for the over-damped Torsion Pendulum analogy of van Egmond, Groen & Jongkees (1949) and could not explain findings (a) and (b) To explain these results on the basis of cupula deflection it would be necessary to assume that the stiffness of the cupula increases during prolonged constant angular acceleration Van Egmond *et al* have proposed (1949) that events within the endorgan either bioelectric, biochemical or plastic change within the cupula, could account for secondary responses, and this possibility cannot be ruled out Lowenstein (1956) has reported that increasing cupula deflection in elasmobranch initiates neural activity "in one after the other previously silent units which often adapt themselves rapidly Adrian (1943) and recently Melvill Jones (1967) recording from the vestibular nuclei in cats found little evidence for rapid adaptation However Cappel (1966) has noted that slow declines in some units recorded in the vestibular nuclei of cats correspond temporally to declines in human subjective data The possibility that there is a diminished sensory inflow during prolonged cupula deflection in cats remains open

In man one aspect of the vestibular reaction (subjective velocity) declines while another aspect (nystagmus) does not decline during prolonged acceleration (Guedry & Lauver 1961) From this, it does not seem reasonable to attribute the decline of the one response to a suppression of sensory inflow (Some reservations are necessary in this interpretation because average curves of different groups of subjects form the basis of the conclusion Subjective and nystagmic data from the same subjects should be compared and studied for the presence of correlation) Aschan & Bergstedt (1955) have evidence which implicates the central nervous system in secondary responses Prolonged primary responses induced by unilateral caloric stimulation should provide an opportunity for adaptive changes within the cupula yet Aschan & Bergstedt (1955) reported little or no secondary nystagmus with unilateral caloric stimuli whereas bilateral hot/cold caloric stimuli and rotational stimuli yielding primary responses of equivalent length, produced secondary responses

Although secondary nystagmus (and apparently associated response modulation) in man and cat are probably attributable to the central nervous system, it remains quite possible that some of the differences between man and cat are attributable to differences in the properties of endorgans e g the shorter primary nystagmic response in cats (irrespective of stimulus duration) is probably attributable to a greater cupula springaction in cat Response parameters of the central nervous system may be conditioned or inherently matched to the response parameters of the cupula-endolymph system so that the shaping of responses to unusual stimuli may be similar in form but on a different time base in different animals.

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ACKNOWLEDGMENTS

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RESUMÉ

Un rapport direct entre la durée d accélération et a) le déclin de réponse pendant l accélération b) le cours de déclin de réponse après l accélération et c) grandeur de la réaction secondaire est regardé comme indice d'un procédé central qui limite une réaction vestibulaire primaire prolongée Ce procédé se manifeste par son influence sur des réactions réflexes relativement élémentaires (nystagmus) chez les chats et se manifeste d'une manière frappante chez les hommes par son influence sur la perception sensorielle

ZUSAMMENFASSUNG

Eine direkte Verwandtschaft zwischen Dauer der Beschleunigung und a) Verminderung der Reaktion während der Beschleunigung, b) Grad der Verminderung der Reaktion nach Beschleunigung und c) Ausmass der Sekundärreaktion werden als Zeichen eines zentralen Vorgangs, der eine andauernde vestibulare Primärreaktion einschränkt betrachtet Der Vorgang offenbart sich durch seine Einwirkung auf die verhältnismässig grundlegenden Reflexreaktionen (Nystagmus) der Katzen und ist bei Menschen durch seine Einwirkung auf die Sinneswahrnehmung mehr ausgeprägt

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RÉSUMÉ

Un rapport direct entre la durée d accélération et a) le déclin de réponse pendant l accélération b) le cours de déclin de réponse après l accélération, et c) grandeur de la réaction secondaire est regardé comme indice d'un procédé central qui limite une réaction vestibulaire primaire prolongée Ce procédé se manifeste par son influence sur des réactions réflexes relativement élémentaires *(nystagmus) chez les chats et se manifeste* d'une *manière frappante* chez les hommes par son influence sur la perception sensorielle

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1966) Such dimensional changes suggest a degree of local action of tones on the basilar membrane.

Electrophysiological studies especially with the method of cochlear potentials, also give indications of functional improvement of the auditory receptors in several species of lizards (Wever *et al.*, 1965) In many Gekkonids, for instance the sensitivity has reached a high degree over a wide range of tones and extends to the high tones, up to 10 kc/s. However the resemblance to the mammalian ear is not perfect in view of the non linearity observed by Wever and associates (1963, 1964) in several species Under normal conditions, in higher vertebrates, the cochlear potentials increase in amplitude as a linear function of sound intensity at higher sound levels they depart slowly from linearity and finally reach a maximum In most lizards this is not the case but the intensity functions show dips, plateaus, and irregularities that are difficult to interpret in terms of mammalian cochlear mechanisms.

In the present study the first goal is to describe the main aspects of the nonlinearity observed in the cochlear potentials. A second aim is to find some new indications of differentiated mechanisms in this ear

The Tokay gecko was chosen for these experiments because this species clearly shows the presence of nonlinear mechanisms and belongs to a family of lizards with one of the most highly developed inner ears The Tokay gecko has a relatively large number of hair cells, about 1600 and the basilar membrane on which the papilla rests has a tapered shape, being three times wider at the ventral than at the dorsal end (Wever 1965 Miller 1966)

METHOD

Subjects

In these experiments 36 Tokay geckos were used These specimens varied fairly greatly in ize and weight. They measured over-all 26–48 cm, and 18–24 cm from snout to vent, and weighed 42–144 g. The sex of the subjects was not individually determined

In sthe ia

Animals in acute experiments were anesthetized with 5% or 10% Ure thane (ethyl carbamate) in Ringer s solution, injected intraperitoneally The d se was 0.04 or 0.02 cc per gram of body weight, respectively Animal used in chron xperiments, in whi h the ighth nerve was sec t oned or deafnes produced by verstimulation, were anesthetized with Nembut l (50 g ml) u ing 0.06 cc per gram of body weight intraperitone- lly and mall doses were added during the experiment to maintain a deep lev l of anesthesia In some anim ls Fl xedil (Galamin triethiodide) in a dosage f 100 mg per cc was injected intraven u ly at a rate of about 0.5 cc per hou t cut ff the activity of th middl ear muscles. In thi

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PATTERNS IN THE COCHLEAR POTENTIALS OF THE TOKAY GECKO (*GEKKO GECKO*)

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The nature and origin of the nonlinearity in the cochlear potentials of the lizard *Gekko gecko* are investigated. Potentials recorded from silver ball electrodes on the round window and in the cochlea are averaged in an on-line computer and measured on a wave analyzer. The waveform of the potentials follows the frequency of the stimulating sound at low intensity and appears in general as a frequency doubling. Fourier analysis of the potentials reveals a second harmonic that is often larger than the fundamental, depending on the frequency of the stimulating sound. Action potentials, middle ear structures, and middle ear muscles contribute to the distortion only to a small degree. This distortion must thus arise in the inner ear structures. Differences between potentials from two sites of recording support this hypothesis. The findings are analyzed in comparison with mammalian cochlear potentials and discussed in relation to anatomical characteristics of the auditory structures of the *Gekko gecko*.

INTRODUCTION

Among the vertebrates, the reptiles are the first in the evolutionary scale that have an inner ear with a separate and well defined cochlear duct. In view of the close relation of the present day reptiles to the stem reptiles which gave rise to mammals and birds, this fact raises interesting questions of phylogenetic and physiological nature. The structure and function of the ear of reptiles have been the object of several studies in which one has looked for characteristics typical of a new step in evolution and with resemblance to the mammals.

Anatomical studies have disclosed a great diversity in the shape, the length and the detailed parts of the inner ear of reptiles, especially in the family of lizards. Indeed, cochlear structures of lizards can be extremely primitive or may show on the contrary some features of the mammalian cochlea, such as progressive changes in the dimensions of the basilar membrane and therefore in its mechanical properties (Wever 1965, Miller

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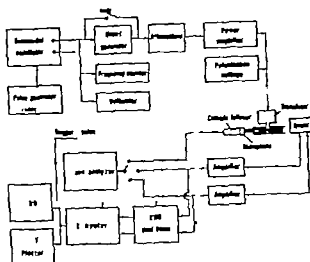


FIG. 1 General diagram of the stimulating and recording set-up. *Note 1* Pulse generator used t determine duration f tone burst. *Note 2* Switch used for continuous tone stimuli

pseudo-experimental situation (orifice of the sound tube closed by a piece of clay which approximated the drum membrane) The curve was flat up t kc s and above this frequency it dropped by 30 dB in one octave. The linearity of the sound system was checked by measuring the sound level at all settings of the attenuators used in the experiments. Second harmonic di tortion was measured on a wave analyzer at high sound levels, and reached 10% around 10 dynes cm at low frequencies (Fig. 2) Above 1000 s the transducer was capable f producing higher sound levels with mall r distortions. These measurements are very similar to Anggård s xcept for a resonance in the system at 2000 c/s which increased the h rmonic distortion for a tone of 1000 c/s. The amount of third and fourth harmonics wa negligibl at the sound pressures used in the experiments (10 dynes cm m ximum)

In som experiment where extremely loud sound were necessary a Western Electric 555 speaker was used This peaker can produce sounds f 1000 dynes cm with negligible distortion.

Condensation and rarefaction licks were produced by driving the elec t oacoustic t ansducer with a square wav of 0.05 msec duration from a timulator Calibration of peak sound level with the click stimulus was bt ined by connecting a inch Brüel and Kjaer (type 4135) condenser microphon into an acou tic coupling ch mber of small olume fitted on the n l of the sound tube The distance between the diaphragm of the monitoring microphone and the end f the sound tube was 2 mm a dist nce which pproximated the separation between drum nd sound tube Th output f th monitoring microphone was di played on a cathod ray

case the animals were tracheotomized and artificially respirated. For these animals the electrocardiogram was monitored as an indication of the state of the animal

In all experiments the body temperature was measured with a thermistor probe placed in the vent and it was kept constant at 27±1 C by a thermostatically controlled DC regulated heating pad

Surgical procedure

The surgery was performed under a binocular dissection microscope Since in the lizards the middle ear cavity is part of the pharynx the round window was approached by an opening in the lower jaw close to the posterior end of the mandible The hyoid bone was removed by careful dissection on one side except in chronic animals in which the opening was made as small as possible and the hyoid bone was spared to allow quick healing The masseter muscles and the trachea were slightly retracted to facilitate the approach to the round window which was cleaned of all mucus

In some animals in which intracochlear recordings were made a small opening was drilled in the lateral wall of the otic capsule, just ventral to the stapes, and a small bead electrode was introduced in it Since the hole was tiny 0.27 mm in diameter very little perilymph escaped from the scala vestibuli

Sound stimulation

A general diagram of the stimulating and recording set up is shown in Fig 1 The animal was placed in a sound insulated and electrically shielded room The sounds were delivered to the drum membrane in a closed acoustic system that was sealed over the external auditory meatus with petroleum jelly or a ring of modeling clay

The sound source was a Brüel and Kjaer 1 inch microphone (type 4131) fixed to a plastic tube following the dimensions given by Anggård (1965) A polarization voltage of 220 V DC was applied to the condenser microphone The electrical sinusoidal signals were produced by a signal generator They were accurately attenuated and amplified A probe tube inserted in the center of the plastic sound tube led to a microphone in order to measure the sound pressure at the end of the sound tube close to the drum

Most of the experiments were performed with continuous pure tones, but in some of them tone bursts were used by triggering the signal generator with pulses from a stimulator In this case an onset generator producing a regular increase and decrease of the amplitude of the sinusoidal signals was introduced between the signal generator and the attenuators Rise and fall times were generally 10 to 20 msec to avoid transients.

The frequency characteristics of the sound system were tested in a

range of the computer was extended by the use of a Northern Scientific type 303 microsampler which yields good resolution *above 1000 c/s*. The output of the computer was displayed on an X–Y plotter and on the face of an oscilloscope

Cathode ray oscilloscope and computer were time locked to the sinusoidal stimulus by a triggering signal from the sinusoidal oscillator when *continuous pure tones* were used When clicks or tones bursts were used, the triggering signal was provided by the stimulator

RESULTS

It is now generally accepted that the cochlear potentials are generated in the hair cells and that they play an important role *in the early stage of* sound perception Therefore it was desirable in the Tokay gecko to analyze thoroughly the following main characteristics of these potentials sensitivity to a large range of tone frequencies, waveform of the potentials, increase of amplitude following an increase of sound intensity locus of distortion, and responses to transient sounds. The data gathered on these various points will be presented successively here

1 *Sensitivity*

The sensitivity has been determined by presenting various tones at the sound pressure necessary to produce a response of 0 1 μv RMS. When the ambient noise (noise in recording equipment and biological noise) was too high, values greater than 0 1 μv were used as criterion. In such cases the sound pressures were calculated to indicate the level that would be necessary to produce a cochlear potential of 0 1 μv In the lizards an effort was made to avoid this technique which is common in mammals because of the nonlinearity appearing even at low intensities. Responses were obtained over a range from 100 c/s up to 6 kc/s in general, in some cases up to 10 kc/s. The sensitivity was measured for the whole range of frequencies only in a few cases, and most of the time only *certain frequencies* were chosen. For this reason the mean sensitivity curve (Fig 4 Group II) displays for each frequency the average of groups with different numbers of subjects, varying from 2 to 21

This mean sensitivity curve reveals some differences from the one published on five Tokay geckos by Wever and associates (1963) represented as Group I in Fig. 4 although it is very *similar in shape* The present subjects show a greater sensitivity than the previous ones without the sudden decrement around 1.5 to 2 kc/s. These differences can be explained by the care given in this study to place the electrode on the round window membrane and not on the contiguous bone The potentials were also picked up by an electrode of a slightly larger diameter to enlarge the surface of contact

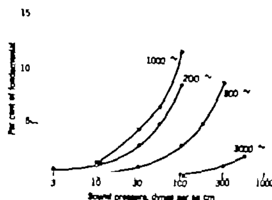


Fig. 2.

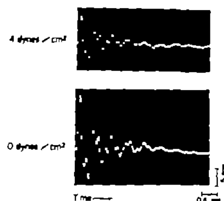


Fig. 3.

Fig. 2 Second harmonic dist rti n in the sound g nerating syst m.

Fig 3 Waveform of the raref cti n acoustic click fo two lev ls of output Negativity upward.

oscilloscope and the peak amplitude was measured Owing to the excellent pulse response of the $^1/_4$ inch microphone the peak sound level could be determined directly by using the calibration supplied with the microphone (Fig 3) No wave differences (except inversion) were observed between condensation and rarefaction clicks By increasing the intensity of the click or the duration of the electrical square wave changes in amplitude of the first peak occurred but not in the steepness of its slope

Recording

For the study of auditory functions by the method of cochlear potentials, a silver bead electrode, about 0 5 mm in diameter was placed on the round window membrane The potentials were picked up between this active electrode and a reference electrode clamped on the headholder In some experiments the cochlear potentials were also picked up from the scala vestibuli at a point close to the stapes In these cases silver bead electrodes of about 0 1 mm in diameter were used to fit a hole drilled in the lateral wall of the otic capsule

As shown in Fig 1 the potentials were amplified in a Tektronix 122 low level AC coupled, differential amplifier The frequency response was limited to a band between 80 c/s and 10 kc/s. The signals were measured in a wave analyzer which acts as a selective voltmeter with a 3 cycles band width The narrow band noise in the equipment as measured n the wave analyzer was normally 0 02 v RMS with the input to the amplifier shunted with a 5 kilohm resistor

Simultaneously the potentials were displayed in a cathode ray oscilloscope and fed into a Northern Scientific type 544 average response computer The vertical output of the cathode ray oscilloscope was used for additional amplification of the signals to the computer The frequency

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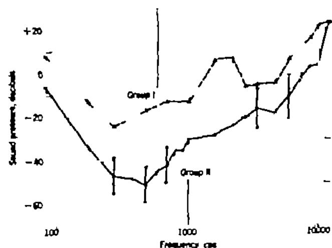


FIG 4 Mean sensitivity curves in two groups of *Gekko gecko* shown as the sound pressure in dB relative to 1 dyne/cm² required to produce a standard response of 0 1 μv RMS Vertical lines show the st ndard deviation, computed fo points representing 10 or more mea urements The electrodes were all on th round wind w

The possibility of electrical radiation from the sound source has been checked in animals in which the cochlea was no longer responding after injury to the blood supply to the cochlea In these cases no signal could be detected from the round window membrane at sound pressures higher than those normally applied in the experiments.

Since the Tokay gecko like many other lizards can live for several days under Urethane anesthesia, experiments were often continued over at least two consecutive days. The sensitivity was checked each day and the variations never indicated a particular trend towards an increase or decrease of sensitivity The variations rarely exceeded 10 dB

2 Waveform

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In the Tokay gecko these averaged potentials had a sinusoidal form in agreement with the frequency of the stimulating tone only at low sound pressures and only for some frequencies (see Fig 6 p 14) Under most conditions these potentials appeared greatly distorted and often with a frequency double that of the applied tone This type of dist rtion varies in degree from subject to subject but exists in all of them

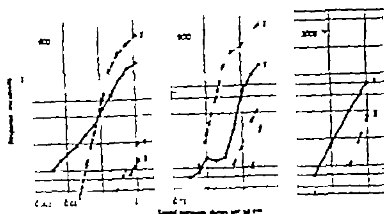


Fig. 5 Intensity function (in μ RMS and harmonic pattern for the cochlear pot ntial to 3 pure tones. Each curv bears mber indicating it order in the harmonic series. Not the absence of 2nd nd 4th harmonics for 2000 s. Gekk geck D 6")

In some geckos cochlear potential were observed while the animals were dying and during the first hour fter death, in order to follow their modifi cations. In these subject death was caused by injecting a large dose of Flaxedil (Galamine triethiodide intravenously to stop breathing and heart beat, or by clamping the ascending aorta. Under these condition the cochlear potentials decreased in amplitud after death, as has been shown in mammals (Davis *et al.*, 1934 Wever *et al* 1941) but the double-frequency wavef rm remained unchanged.

3. *Intensity functions and distortion measurements*

In order to obtain numerical values for the distortion in the ear the amplitude of the cochlear potential at the fundamental frequency and at its harmonic frequencies wa measured as the sound was increased in steps of 5 or 10 dB. In Fig. 5 intensity functions are represented on a double logarithmic plot for three timulating frequencies and their har monics. From this figure it appears clearly that the increase of amplitude at the fundamental frequency bears no linear relation to the inten ity of the stimulus, as had been found by Wever and collaborators (1063) Thi is in particular true for low frequencies while at higher ones (2 kc and abov) a trend toward linearity exists.

Another important fact revealed in thi figure is th large amplitude of the second harmonic at nearly all stimulating frequencies except the highest ones The second harmonic appears sometimes at low levels of the sound stimulus, that is, at about the sound pres ure required for a funda mental of 0.1 μv or sometimes at 10 o 20 dB above this alue Its rise in magnitude bears generally a linear relationship to the sound pres ure up to 1 dyne/cm² ± 10 dB then lowly departs from linearity This second harmonic tend to reach and surpass in amplitude the component for the

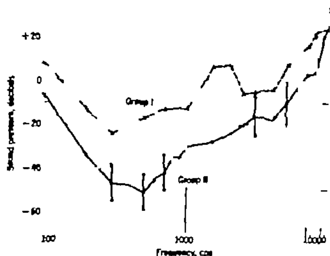


FIG. 4. Mean sensitivity curves in two groups of *Gekko gecko* shown as the sound pressure in dB relative to 1 dyne/cm² required to produce a standard response of 0.1 μ RMS. Vertical lines show the standard deviation, computed for points representing 10 or more measurements. The electrodes were all on the round window.

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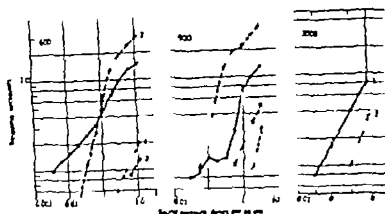


Fig. 3. Intensity function (I μv RMS) and harmonic pattern for the cochlear potential t 3 pure tones. Each curve bears number indicating the order in the harmonic series. Note the absence of 3rd and 4th harmonics for 3000 c s. (G 33 gecko D 67)

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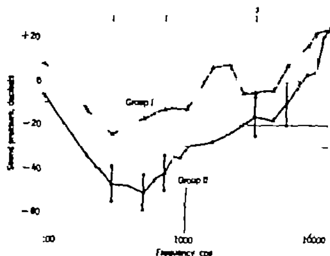


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A. *Contamination from the Nerve Action Potentials*

It is known that in mammals the acti n potentials of the eighth nerve often occur during the positive half cycle of the cochlear potentials on the round window or when the cochlear potentials are going from negative l positi e (Rosenblith & Rosenzweig, 1952 Leake & Kiang, 1962) Since the r und window i as close to the fibers of the cochlear bundle a to the ba ilar papilla in the T kay gecko, it i possible that nerve acti n poten tials may be mixed with the cochlear responses and partly responsible for the strong second harmonic and for the double-frequency waveform observed.

To test this possibility an attempt wa made to section the posterior branch of the eighth nerve in I ur animal Six weeks after the surgery a control experiment was performed and the animal wa then prepared for histological examination In one case the section was successful, a could be judged from the responses to clicks (Fig 6)

The cochlear potentials did not change in waveform except at 200 c/s and a quantitative analysis of the distortion did not reveal any impr ve-ment in linearity ix weeks after th section The only postdegenerative modifications speak in favor of an increase rather than a decrease of the amplitude of the second harmonic for all the frequencies, except f r 200 c s. These results correspond t mammalian studies in which the action potential contaminate only the low frequencies where a large number of nerve fibers can fir in synchrony with each wave of the sound stimulus (Rawdon Smith & Hawkins, 1939 Wolsk, 1964)

B *Action of the Middle Ear Mu cl s*

Wever and associates (1964) found that in *Hemid ctylus gecko* the l wer part of the inten ity function lost some of its irregularities after intraperitoneal injection of a curarizant (Intocostrin) to suppress muscle activity However the sl pe of the inten ity function failed to attain linearity under this condition A moderate dose of Intocostrin was used by these uthors to avoid a cessation of the respiration

In order t understand accurately the role of the middle ear muscles in the irregularities of the inten ity functions, muscle activity shoul l be completely suppressed For thi reason these experiment were repeated with continuous intravenous injection of Flaxedil (Galamine triethiodide) on several animals that were artificially respirated. It was generally as-sumed that the Flaxedil was acting when the respiration was noticeably lowed down or stopped altogether and when the natural rhythm no longer opposed th respirator

Some results for one animal with 24 hours of continuou injection of Flaxedil ar di played in Fig 7 The intensity functions for low and high frequ ncies tended to be more linear at low sound pressures, because of a

TABLE 1 *Second harmonic in per cent of the fundamental in the cochlear potentials recorded from the round window*

Means of 4 to 7 measurements.

Frequency (c/s)	Sound pressure in dynes/cm² 0 1	0.3	1	3	Remarks
200	95	183	295		Great distortion
290	48	105	261		
400	283	137	426		
500	157	280	380		
600	138	265	190		
00	219	222	334		Extreme distortion
800	209	379	676		
900	193	306	338		
1000	129	283	360		
1500	62	147	226		
2000		85	96		Slight distortion
3000		58	68	127	
4000		22	41	100	
5000		58	54	167	
6000			34	77	

fundamental frequency Table 1 gives numerical values of the second harmonic expressed in per cent of the fundamental and shows clear differences between groups of frequencies the distortion is much more pronounced for the middle than for the high tones.

Higher order harmonics appear at high sound pressures, that is, around 1 dyne/cm² and very often rise suddenly Their slopes are steep and their amplitudes remain smaller than the fundamental They behave as would be expected from the mammalian studies on distortion very differently from the behavior of the second harmonic in the gecko At frequencies higher than 1500 c/s, these harmonics are very small or unmeasurable at the sound pressures applied in these experiments

These observations lead to the conclusion that the nonlinearity of the cochlear potentials in the Tokay gecko is produced by the generation of a strong second harmonic, which does not seem to belong to the distortion pattern described in various higher vertebrates (Wever & Lawrence 1954)

4 *Origin of the distortion*

The next step of this study was to investigate the origin of this double frequency or strong second harmonic The following possibilities were considered contamination of the cochlear potentials by neural action potentials action of middle ear muscles, the role of the middle ear structures in sound transmission, and distortion generated in the inner ear

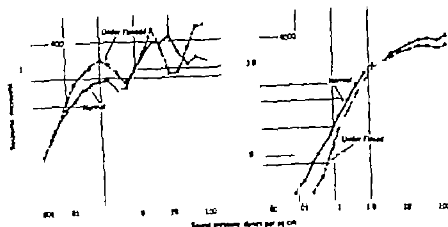


Fig. 7 Effect of curarization on intensity functions (1 μ RMS) f two tones. (G kko geck D 21)

monic were taken in these experiments for methodological and technical reasons.

In these experiments, although the doses of Flaxedil were so large that in mammals they would have suppressed muscle activity t tally (Wer sill, 1958) irregularities were till observed in the cochlear potentials. This fact suggests that the middle ear muscles are not responsible for the nonlinearity

C. Role of the Middle Ear in th Transmission of Sound

The middle ear s a locus of production of harmonic di tortions has been excluded in mammals on the basi of a number of experiments (Wever *et al* 1938, 1940 1941 von Békésy 1960 *a*) In most lizards the middle ear consist of two parts the cartillagenous extracolumella an l the bony columella ending in a footplate in the oval window Because the pattern of distortion in the Tokay gecko is very different from that in mammals, th question arose whether the very imple and primitive ossicular system could account for the nonlinearity observed Two experiments were performed to investigate this problem.

( ) Afte recording the mplitud of the fundamental and second harmonic under normal conditions, the columella was sectioned first, then th drum and ossicles were removed. After each step of the surgery measurements of cochlear responses were repeated They did not show any important modifications, either in linearity or in distortion pattern when the decrease in sensitivity was compensated for by increasing the stimulus intensity

(*b*) In the second experiment, fter the usual measurement of sensitivity and determin tion of the intensity functions, the drum and colum lla

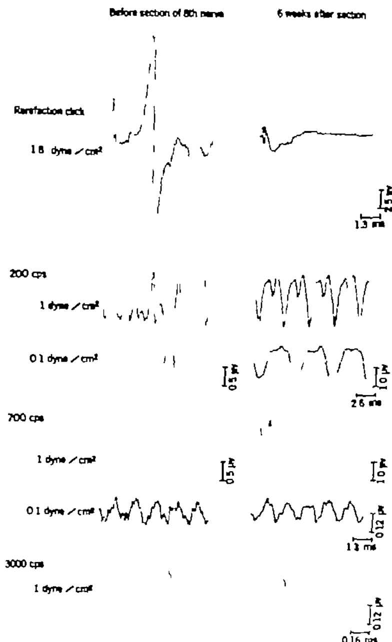


FIG 6 Wa ef rms (av raged) of th ochlea pot t al nd f the respo es t licks before nd afte 6 week of deg nerati n. Amplitude μ peak-to-pe k timulation rtefact (*Geck gekk* D 49)

reduction of the biological noise which allows more reliable measurements However for 400 c/s (and also other frequencies) there was a bending over of the curve at 0 1 dyne/cm² followed by a second increase of ampli tude that was not suppressed by curarization Such a function is still dif ficult to explain if the first bending represents a real maximum a further increase of the sound pressure should produce impairment of the hair cells and loss of sensitivity (Wever & Lawrence 1954) This was not the case here and even after greater sound pressures were applied the measure ments could be immediately reproduced No readings of the second har

this impedance is not known the two sets of results can only be compared in terms of cochlear potential

At low frequencies the result d n t show great differences between mea urements with the mi ldle ear intact and those with vibratio n of the footplate From 1000 c/s upward the second harmonic i always present but is much maller for mechanical vibration than for air borne sounds. More information i still needed to account f r this phen menon which may be related to the coupling of the vibrator to the mechanical system of the ear as well as to characteristics of the ossicular chain

D *Origin of the Distorti n in the Inner Ear*

Since the irregularities and nonlinearity of the intensity functions are due only in minor degree to a contamination b nerve potentials, to the acti ity of the middle ear muscles, and to the behavior of the middle ear ystem, the strong second harmonic must arise in the structures of the otic capsule probably in the cochlear duct.

This hypothesis was supported by recordings from different locati ns in the cochlea. In three animal the cochlear potentials were recorded simul taneously from electrodes on the round window and in the scala vestibuli, ventral to the footplate of the columella. Systematic differences in sensitivity frequency range and am unt of di tortion were observed in these experiment

The differences in sen itivity are shown in Fig. 9 For all low tones, less sound pressure wa needed to record responses of standard amplitude from the scala vestibuli At high frequencies, on the contrary the sound intensity had to be increased in order to get the standard cochlear pot ntial

The potentials from the scala vestibuli were much more sinusoidal in shape than those from the round window Only at higher levels of sound about 1 dyne cm distortion appeared and it never became severe enough to give th appearance of a frequency doubling.

The intensity functions measured from the scala vestibuli also appeared much mor regular and linear The maximums were larger except for frequencies abov 2 kc s. The harmonic pattern resembles that f mammals, since the second harmonic ppears only at higher levels of sound, grows linearly nd reaches a maximum which is always smaller than that of the fundamental (Table 2)

Differences of phase were observed between the signal recorded from the round window and those from the scala vestibuli Under the conditions of these experiments, the phase difference wa generally smaller than 180 degrees and varied with frequency and intensity

To summarize the differences described are important from several points of view Possible variations in impedance of the two recording sites can account for some of them, such as the differences in sensitivity However in the recordings from the scal vestibuli the large differences in

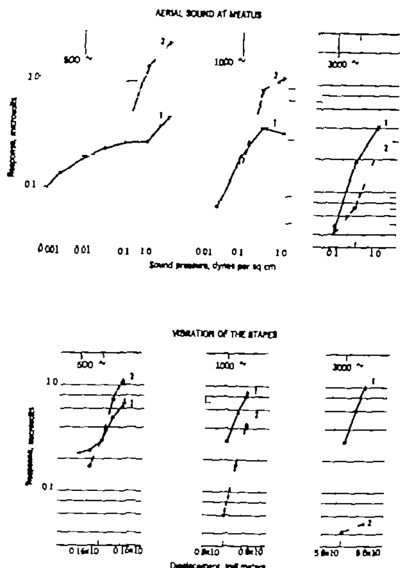


Fig 8. Intensity functi n (in μv RMS) f r cochl ar responses to to es f different frequ ncies with rial sound applied t th e ternal uditory me tus and with ibra tion f th stapes (1) Fundament l (2) 2nd harm ni (G LL g k D 60)

were again removed up to the footplate of the columella The footplate was vibrated with a Goodman vibrator which had been thoroughly shielded and checked for electrical radiation The displacement amplitude of the vibrator was measured optically with an M T I Fotonic Sensor The amplitude of the vibration was increased until a reading corresponding to a previous measurement of the cochlear potentials was reached From there on the amplitude was increased in 5 or 10 dB steps and the waveform was displayed on the computer In Fig 8 the magnitude of the cochlear potentials is shown in microvolts as a function of sound pressure and also as a function of the vibratory displacement of the footplate Because the displacements of the drum membrane and the columella under the action of sound pressure depend upon the impedance of the mechanism and since



Fig. 10 Averaged responses t condensation and rarefaction licks, recorded from the round window Amplitude in μ peak-to-peak. Repetition rat 1 sec (Gekk gek. D 65.)

ward movement of the drum and con ersely it is negative for a condensation click

In the Tokay gecko, both condensati n and rarefaction click produce a positi potential on the round window followed by a large negative-to-positive action potential, as shown in Fig. 10 This positive potential which rem ins after sectioning of the eighth nerve increases in amplitude in a line r relation to the intensity of the clicks, becomes sharper and narrower and assumes the form of a spike at high intensity Its latency (taken as the delay between the stimulus artefact and the foot of the wav) v ries from 0 4 msec around 1 dyne cm to 0 13 msec at 10 dynes cm No systematic differences appear between the latency of the responses t condensation and rarefaction clicks.

This positi e potential changes to negati when it is picked up from *th scala estibuli. This correspond to the reversal of polarity already* observed in the potential with pur tone stimuli, and well known in mammals (Tasaki *t al.*, 1952)

DISCUSSION

Conc rning the nonlinearity observed by Wever and associates in th cochlear potential of the Tokay gecko, the present stud has disclosed four main points which may lead to an explanation of this phenomenon

First, in responses to pure ton stimulation an important distortion exist

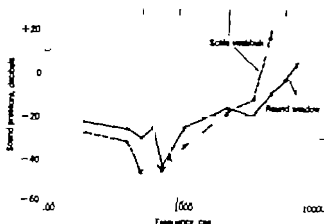


Fig. 9 Sensitivity curves from two recording sites. (*Gekko gecko* D 47)

sensitivity for the high and low frequencies raise the question whether this electrode may be in a favorable position to pick up the activity of a structure especially tuned for low tones, either the more ventral part of the basilar papilla or the lagenar macula.

5 *Responses to transients*

In mammals it has been shown that a transient sound such as a click produces a train of electrical waves (Rosenblith & Rosenzweig, 1952 Peake & Klang 1962) In recording from the round window the first wave is positive in the case of a rarefaction click which produces an out

Table 2 *Amount of second harmonic in per cent of the fundamental for the cochlear potentials recorded from the round window and from the scala vestibuli for various tones and sound pressures* (*Gekko gecko* D 47)

Frequency (c/s)	Sound pressure in dynes/cm				
	0 03	0 1	0 3	1	3
400					
Round window		0	35	276	
Scala vestib li		0	9	30	
600					
Round window	0	160	400	255	
Scala vestib li	0	34	57	56	
1000					
Round window	0	33	103	440	
Scala vestibuli		0	26	65	
4000					
Round window				39	46
Scala vestibuli					100

results obtained for very low intensities under Flaxedil which greatly reduced the biological n ise However two fact cannot fit into this framework first it is impossible to assimilate the pattern of distortion mea ured in geckos to that obtained in mammals. The exi tence of a strong second harmonic which i much larger than the fundamental, seem to belong specifically to the inner ear f the Tokay gecko and perhaps f other lizards. Secondly it was possible to increase the sound inten ity after having reached the overloading region and still record a new increase f amplitude without prov king any temporary or perman nt threshold hift indicative of damage as would always occur in mammals.

Unless the mechanisms of harm nic distortion differ in the lizard's cochlea from that of mammals, it seem that the di tortion hypothesis may account only for a small part of the action peculiar t thi ear

2. *Two-structur s Hypothesis*

According to the observations on the anatomy of the cochlear duct and the morphol gy of the ba ilar papilla in the T kay gecko, it may well be that cochlear responses mea ured at the round wind w are the sum f potentials arising in tw different populati ns of hair cell The pos ible realizations of this mechanism will be described and their functional roles discussed.

(a) *Effect of inten ity on receptor respon e*

In the organ of Corti of mammals, greater sensitivity ha been attributed to the outer hair cells than to the inner ones, on the basi of their position on the ba ilar membrane their atta hment to the tectorial memb rane and their usceptibility to injury (Davis *et al* 1953, 1958 von Békésy 1960 *a*)

In the Tokay gecko the di tinction between inner and uter hair cell does not exi t, but hair cells differ in their relation to the tectorial membrane (Fig. 11) The cells attached to it by mean of fiber connection and finger-like processes, which act as a restraint and *ten ion on them may* be readily stimulated at low intensities. On the contrary the other group of cell connected to the sallet may be stimulated only at high inten i ties, since this structure i nearly independent of the tectorial membrane *and act* *nly through its own inertia* A certain time delay and phase shift may lso exist between th stimulation by the "sallet" and by the finger l k process (Wever 1960)

The present study has d monstrated that the cochlear potential generally ha e normal wavef *rm* at low intensities which probably reflect only th activity of one group of hair cells. The strong second harmonic which appears at slightly higher sound levels *might then be due to th* simultaneous action f tw groups of hair cells, the first one acting non linearly and the ther still linear but with phase shift The *fact that*

in the cochlear potentials, especially a large second harmonic which sometimes exceeds the fundamental component

Secondly since the sound source the middle ear and the nerve activity can be largely excluded *as the origin of the distortion the structures of* the inner ear may be considered as the principal source

Thirdly the pattern of cochlear responses to sound varies within the cochlea according to the location of the active electrode relative to the inner ear structures

Finally an unusual feature has been noticed in the responses to clicks, which induce a positive potential on the round window regardless of the polarity of the click

These four points show that the function of the ear of the Tokay gecko differs in many aspects from that of higher vertebrates In mammals and birds indeed it is well known that the cochlear potentials at ordinary levels reproduce the waveform of the stimulus Only at high levels of sound does harmonic distortion appear and the waveform of the potential is somewhat altered as overloading occurs At the highest sound levels the total overtone content represents only a little more than 50% of the size of the fundamental In response to transient stimuli the receptor potentials recorded from the round window are always positive with an outward movement of the drum and negative with an inward movement

Although no full explanation of the special cochlear patterns of the Tokay gecko can be given at this time, it is possible to formulate several hypotheses about the possible mechanisms in this ear in relating functional observations with anatomical structures and their characteristics Among these hypotheses, two will be discussed here The first relates the existence of the distortion to the small number of hair cells. The second examines the possibilities of two structures reacting to sound stimulation

1 *Distortion*

According to the volley theory (Wever 1949 Wever & Lawrence 1954) each tone has a wide operating area on the basilar membrane with a site of maximal stimulation When the increasing sound pressure reaches a certain level the action of the hair cells becomes nonlinear first at the site of maximal stimulation and then around it If the sound is increased beyond the overloading point, irreversible injuries occur

The basilar papilla of the Tokay gecko has in comparison to mammals a very small number of hair cells This implies that this structure may function with a linear relationship to sound pressure only at low levels of stimulation Most of the linear portion of the intensity curves would be b low cochlear potentials of 0 1 μV amplitude and lost in the general noise Therefore at the levels of sound used in the present experiments potentials should be extremely distorted and close to overloading

Some data seem to confirm this hypothesis, namely the more linear

results obtained for very low intensities under Flaxedil which greatly reduced the bi logical n ise However two facts cannot fit into this framework. first it is impossible to assimilate the pattern of distortion measured in geckos to that obtained in mammals. The existence of a str ng second harmonic which is much larger than the fundamental, seems to belong specifically to the inner ear of the Tokay gecko and perhaps of other lizards. Secondly it was possible to increase the s und intensity after having reached the overloading region and till record a new increase of amplitude with ut provoking any temporary or *permanent threshol l shift indicative* of damage as would always occur in mammal

Unles the mechani ms of harmonic di tortion differ in the lizard's cochlea from that of mammals, it seems that the di torti n hyp thesi may account nly for a small part of the action peculiar to this ear

2 *Two-structures Hypothesi*

According to the observati ns on the anatomy of th cochlear duct and the morphology of the basilar papilla in the T kay geck , it may well be that cochlear responses mea ured at the r und wind w are the um f potential arising in two different p pulati ns of hair cell The p sible realizations of this mechani m will be d scribed and their functi nal rol s discussed.

( ) *Eff t of intensity on recept r respon e*

In the organ f Corti of mamm ls, greater sen itivity ha been attributed t the outer hair cell than to the inner ones, on the ba is of th ir position on the basila membrane their attachment t the tectorial membrane and their susceptibility to injury (Davis *et al* 1953 19 8 von Békésy 1960 *a*)

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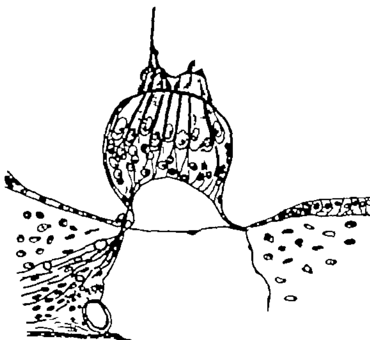


FIG 11 The uditory papilla of the *Gekko gecko* from near the middle of the cochlea. 1100 microns from the d rsal nd Note the exist nc of two co nect1 ns to th tectorial membrane the finger-like process and the sallet Scale × 500 (From Wever 1965.)

responses to high frequency tones do not show as great an amount of distortion speaks in favor of this hypothesis, since the sallet" is located only in the more ventral half of the basilar papilla where low tones are expected to act specifically

Some experiments on the activity of the eighth nerve which will be reported in another paper (Hepp-Reymond, 1968) give further data supporting this hypothesis Histological and electrophysiological results on some overstimulated geckos and data gathered on other species of lizards without the different kinds of tectorial attachment will be of help in testing this hypothesis

(b) Directional sensitivity of receptors

In several structures of the acoustico-lateralis system as the lateral line organs the utricular macula, and the saccular macula, there have been recordings of double-frequency microphonic potentials and of two groups of fibers that discharge during opposite phases of sound or vibration (de Vries & Bleeker 1949 Jielof *et al* 1952 Kuiper 1956 Flock 1965)

These electrophysiological results were related to electronmicroscopical observations, according to which each hair cell is morphologically polarized by the presence of a kinocilium at the periphery of the sensory hair bundle Adjacent hair cells *may have kinocilia pointing in opposite direction* as has been shown in the lateral line organs Therefore under sinusoidal stimulation some cells will be depolarized and some hyperpolarized In a model developed by Flock (1965) depolarization should be always larger

than hyperj larization to explain d uble-frequency j tential Thi ha been pro ed by the fact that in resj onse to tran ient timuli negative potential were always evoked at the recej tors reg r lles f the polarity f the tran ient pulse

In the inner ear of the T k y geck s, the j resence f l oul le-frequency potential and the exi tence of positive potential in the r und win l w in response to click of cpposite polarity l w g ood resemblance t some f the functional properties of the n on auditory lal yrinth Directional sen itivity defined a differenti ti n of the directi n f the li j lacem nt, i very important in lal yrinthin functi on but it seem f n use in hear ing and it i difficult to im gine that th basilar papilla would act in thi w y Nevertheles the tructure f the h ir tuft f the T kay geck as shown by Wever (1965) reveal s me morj h l gical polarizati on (Fig 11 ince the hairs increase in ize j r gres iv ly sometimes t war l the lateral ide sometimes to th medi l wall f the cochlear duct Recent result in electron microscopy f the ba ilar paj illa f the *Cerrhonotu multicarinatus* (Mulroy) reveal the exi tence of a kin ocilium on each hair cell On group of cell appears t be morj h l gically j larized in ne di ecti on, and another group in th pj osite directi n Wever and Mul roy findings lead t the reflection that th ba ilar papilla, which i said to arise from th same structures a th lateral line organs, can till have some remnant of primiti e morphological haracter that are respon ible f th receptors bserved In this case on e n wonder what geckos are ble to hear

(*Cont minati n by pot ntial fr m the lagen r macula*

An ther peculative explanation f l ubl frequency potenti ls invokes the possible role of the lagen r macula This tolithic structure which is lw situ ted in the cochlear duct resembles the utricular macul In lizard it i quite large decreases then in bird and no longer exi t in mammals. In geckos it is greatly ext nded, especially at the ventral end of the cochlea duct, as the studies of Hamilton (1960) and of Miller (1966) ha e shown N thing i really known bout this sensory epithelium to which in fi hes has been attributed directional sensitivity (Löwen tein & Roberts, 1950) in birds vestibular functions (Schwartzkopff 1949) and in lizard auditory functions (Beccari, 1912 Hamilt n, 1963) It may well be that the cell f this macula react to the direction f the displacements of the endolymph by producing microphonic potential that contaminate the recordi gs from the basilar papilla

Con e ning th differentiation f the ear of the Tokay gecko, in terms of local action of the tones on the basilar membran as in mammals, the present tudy cannot bring a definitive answer but describes some phe n mena which trongly support thi hypothesis.

Obviou differences in th cochlear patterns for low and high tones have

been observed in all experiments In particular the second harmonic is much more prominent in responses to low tones up to 1500 c/s (see Table 1) This fact speaks in favor of some differences in the transformation of energy of various groups of tones, which may be related to the fine structure of the basilar papilla In mammals it has been demonstrated that the low tones are more strongly located in the part of the basilar membrane which is less stiff and has a greater mass that is near the apex of the cochlea By extrapolation Wever suggested that in geckos the most favorable place of action for the low tones on the basilar membrane should be the ventral end and for the high ones the dorsal part which is narrower and has less mass

In the discussion on the nonlinearity of the cochlear potentials, it was suggested that it might be explained by the interaction between the activity of two structures From Wever s studies it is clear that finger like processes and sallets act on two different groups of hair cells at one level of the basilar papilla, that is in the ventral half On the contrary in the dorsal region all the hair tufts are connected to the tectorial membrane in a similar way through fiber connections or finger like processes Therefore if the low frequency tones have their sites of maximal stimulation in the ventral part of the basilar membrane and if the sallets (along with the finger like processes) are in the region of the generation of the strong second harmonic, it might be expected that responses to low tones will contain a great amount of distortion High frequency responses would then appear quite linear as in the mammalian ear

The good correspondence of the anatomical observations with electrophysiological findings supports not only the double structure hypothesis but also the theory that different frequencies have specific loci of action on the basilar membrane This suggests that the place principle in hearing appears in the cochlea of some lizard species

In conclusion the results of the present study reveal some complex problems that are far from being solved Electrophysiological investigations of eighth nerve activity selective lesions in the cochlear duct more detailed anatomical data and behavioral studies are still needed before an understanding of the auditory capabilities of the geckos will be reached It seems that the ear of the Tokay gecko is not as simple as formerly believed and cannot serve as a simple model for the mammalian auditory organ albeit there are many structural similarities in the differentiation of the receptors

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ZUSAMMENFASSUNG

Natu an l Herku ft der Nichtlin arit t in len Cochle Potenti len ler Ei-dechse *Gekk geck* wurden untersucht. Pot ntiale mit Silberkugelelektr l n auf d m runden Fen ter un l in l r Cochlea regi triert wur len l l m On Line Computer gemitt lt und a f einem Wellenf rm n lysat r gemessen. Die Form der Potent le folgt der Freque les stimulieren l n Tones für kl ine I tensität und erscheint lt wie eine Frequen erd ppelung. Eine Fourieran lyse der Potentiale bringt in w lt Harmonische hers r. die gewöhnlich vi l grös-ser als l fundament le Frequen l l. Die Aktionspotential d e Strukturen und die M keln des Mitt lohrs tragen nur wenig zu d Dist rtion bei, die deswegen im Inn nohr entstehen sollte. Unterschied zwischen Potentialen die in zw erschiedenen Orten der Cochlea abgeleitet wurden, u terstützen diese Vermutung. Die Befunde werd n mit len Cochlea-Pot ntialen ler Säugetiere vergli hen und in bezug uf natomische Eigenschaften des Inn nohres beim Gekk gecko d sk tiert.

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A STUDY ON THE BIOPHYSICAL CHARACTERISTICS OF THE CAT LABYRINTH

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An investigation was made of the biophysical dimensions of the cat labyrinth. In each semicircular canal the diameter of both membranous and osseous canal and the radii of curvature were measured. From these measurements the length of the canal and its volume were calculated. The volume of sacculus, utricle, endolymph and perilymph were also calculated after measuring the areas in histological serial sections. Distances between canals were also measured and the angles between them were determined. The data were used for calculating the constants of the fundamental differential equation of the cupula-endolymph system.

INTRODUCTION

The fact that most of our experimental work is carried out in the cat and that the biometric data on its vestibular sense organ are incomplete prompted the investigation reported here. The aim was to determine accurately the following parameters: cross-section radius of each semicircular canal and its radius of curvature, the length of each canal, the distances and angles between them and finally some dimensions of other vestibular structures including their volume. Perhaps these analytical data may facilitate the understanding of the *physical model* of the cupula-endolymph system and the action of vestibular stimulation such as that produced by Coriolis forces upon the sense organ of the cat.

THEORETICAL CONSIDERATIONS

The physical model of the cupula-endolymph mechanism as postulated by Lorente de Nó (1927, 1931), Steinhausen (1933), van Egmond, Groen & Jongkees (1949) and others have been considered in our work.

It appears that during evolution as postulated by Jones & Spells (1963) the sluggishness of head movements associated with increase in animal

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$$\Pi = 8\pi^2 \eta R^3 \qquad (6)$$

Therefore

$$\beta_{min} = \gamma_{min} \frac{\varrho}{4\eta} r^2 \qquad (7)$$

or

$$t_{min} = \frac{4\eta}{\psi\varrho} \frac{\beta_{min}}{r^2} \qquad (8)$$

Equation (8) shows that for a given angular acceleration, ψ, the speed of the response t_{min} is a function of both threshold β_{min} and r. Since the speed of the response in a sensory organ is one parameter of its sensitivity, we may define the sensitivity S of a semicircular canal as,

$$S = \frac{1}{t_{min}} \qquad (9)$$

indicating that the shorter is t_{min} the higher the canal sensitivity. Then

$$S = \frac{\psi \varrho r^2}{4\eta \beta_{min}} \qquad (10)$$

This equation expresses that the sensitivity of the semicircular canal is proportional to the square of its internal radius, r, as postulated by Jones & Spells (1963).

The theoretical considerations for the postulate that the time constant of the cupular return is a function of R are the following.

The return angular movement of the cupula after reaching a displacement β_0, is

$$\beta = \beta_0 e^{-\frac{\Delta t}{\Pi}} \qquad (11)$$

The time constant is,

$$t = \frac{\Pi}{\Delta} \qquad (12)$$

The stiffness coefficient, Δ, of the cupula can be obtained from

$$\Delta = \pi \mu r^4 R \qquad (13)$$

(μ pressure exerted by the cupula per unit angular deflection). Therefore

$$t = \frac{8\pi\eta}{\mu} \frac{R^2}{r^4} \qquad (14)$$

Equation (14) shows, as claimed by Jones & Spells (1963), that the time constant of the cupular return is a function of the ratio R^2/r^4. This ratio fulfilled the requirement of their theory that an increase in sensitivity matching the slower head movements of large animals must be associated with a corresponding increase in the time constant of the cupula return.

size was compensated by adapting the canal sensitivity and the time constant of cupula return. They predicted according to Steinhausen's theory of the cupula-endolymph mechanism that changes in the body mass (m) are associated with a proportional change in both the cross section radius, r, and the radius of curvature, R. After statistical analysis of these dimensions in a number of species they postulated that the relation between r or R and m could be expressed in the following equation

$$\log_{10} 100r^2 (\text{or } \log_{10} 100R) = n \log_{10} m + A \qquad (1)$$

where m is in kg, r and R in mm, and n and A are constants.

From theoretical considerations and actual measurements of r and R Jones & Spells (1963) concluded that the sensitivity is dependent on r while the corresponding change in the time constant of the cupular return is dependent on R.

The hypothesis of Jones & Spells (1963) on the adaptation of the semicircular canals to dynamic requirements of the species was later expanded by Mayne (1965). He postulated that the matching of the semicircular canals to the requirements imposed by changes in body mass depend on the range of frequency response and resolution of the system. Mayne indicated that the matching is accomplished by five parameters, that is, radius of membranous canal, radius of its curvature, volume of the ampulla, stiffness of the cupula and number of sensory cells in the crista.

The relation between r and sensitivity of the semicircular canal is expressed in the following considerations. The threshold of excitation as postulated by theoretical developments (van Egmond, Groen & Jongkees, 1949; Groen, 1956, 1957) is reached at a certain angular displacement of the cupula β_{min}. This minimal value depends on the ratio of endolymph moment of inertia Θ to the moment of friction per unit angular velocity Π times the so-called "minimum impulse" γ_{min}, that is

$$\beta_{min} = \gamma_{min} \frac{\Theta}{\Pi} \qquad (2)$$

where

$$\gamma_{min} = \dot{w} t_{min} \quad \text{(Mulder's law)} \qquad (3)$$

where $\dot{w} = dw/dt$ (w angular velocity of rotating device)

$$\Theta \simeq 2\pi^2 \rho r^2 R^3 \qquad (4)$$

(ρ density of endolymph)

$$\Pi = 8\eta\pi R^2 L \qquad (5)$$

(η viscosity of endolymph, L length of canal)

We would like to point out that if the semicircular canal is considered as a complete ring (toroid) then Θ is exactly given by the formula included in Table 11. However equation (4) can be used since $r < R$. Assuming that the length of the canal is one half of a circumference then

FIG. 1. Dorsal, ventral and medial views of the skull (male cat, 5.2 kg) showing diameters whose values are reported in Table 1. *A*, full temporal; *B*, bifrontal; *C*, inter tympanic; *D*, bizygomatic; *F*, foramen-incisors; and *F*, foramen-frontal.

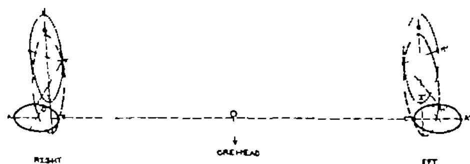


FIG. 2. Diagram of the semicircular canals showing the notation of the distances reported in Table 2. On the right side the solid line *ABCD* represents the horizontal canal, the broken line *EFGH* the anterior vertical canal, and the dotted line *IJK* the posterior vertical canal. On the left side, the corresponding canals are shown.

METRIC CHARACTERISTICS OF CAT LABYRINTH

Two types of observations were made macroscopic and microscopic measurements

A Macroscopic Measurements

1 *Craniometry*

A set of nineteen adult cats of both sexes, weighing between 1 6 and 4.5 kg were taken at random for measuring the diameters shown in Fig 1 The purpose of these measurements was to find out whether the increase in size of the head due to age and sex may be associated with variations in the distances between semicircular canals The measurements showed a large variation in the dimension of both bizygomatic and foramen incisors diameters while the dimension of the bifrontal inter tympanic bitemporal and foramen frontal diameters tended to be more constant (Table 1) Perhaps the size of the head as measured by these diameters or its weight or volume are more important for estimating the phylogenetic adaptation of the semicircular canal sensitivity and time constant of cupular return rather than changes in animal shape and body mass as postulated by Jones & Spells (1963)

2 *Semicircular canals*

The radius of curvature *R* and distances between canals, both unilateral and bilateral are important measurements for the theory of the cupula endolymph mechanism From these measurements other distances or relationship between semicircular canals can be calculated

The distances were determined in seventeen of the skulls mentioned in the previous section In thirteen of the skulls, the periotic capsule was exposed under a dissecting microscope The osseous semicircular canals of each skull were carefully open in their total length that is, from ampulla to their opening in the vestibule Then the skull was rigidly mounted on a Johnson s stereotaxic instrument The di tance between two points on either side and the distance from one point on th right side to the cor

TABLE 1 *Diameters of the sl ull*

Diamete	Skulls (n)	M (mm)
Bifrontal	19	32 8 ± 3
Inter tympa	10	37 2 _ 2 0
Bitemporal	18	42 + 3 0
Foramen-frontal	18	50.0 ± 3.5
Bizygomatic	19	64 1 6 6
F ramen incisors	18	6 7 + 7 3

Fig. 3 Diagram illustrating the projection of the semicircular canals on the horizontal plane. The loci of angles through ... are given in the text. R ... R are the radii of curvature for the horizontal, anterior vertical and posterior vertical canal respectively. The angle ... subtend the arc of the horizontal canal within the utriculus. The values given in the insert were taken from data of Table 2 but the values were rounded off to the nearest integer.

joined forming the common crus (Fig. 4) The distances from various points represented in this figure to the mid-sagittal plane SP can be calculated from Table 2.

B Microscopic Measurements

Histological sections of normal temporal bones were used for measuring the osseous and membranous diameters of each semicircular canal and common crus, and also for measuring cross-section areas of various vestibular structures. From this data the radius and volume of the structures were then calculated.

For measuring the membranous and osseous diameters, serial sections of temporal bones were used. Each section was projected onto a white surface at a magnification of 71 : 1 and diameters measured with a calibrated ruler. The distortion produced by the amplification was so small that no correction factor was used.

The measurements of areas were done in the temporal bones of two cats (A 1371 and B-252) by projecting (71 : 1) upon a cardboard the vestibular area of each section. The outlines of different structures were carefully traced and their area measured with a planimeter. In cat A 1371 one every five sections and in cat B-252, one every ten sections were drawn through out the temporal bones of both sides. These areas were used for calculating

TABLE 2 *Averages $\bar{x}$ in mm of bilateral and unilateral distances between canals*

See Fig 2 f r identification f segm nts represented by capital letters. n = Number f observations.

Horizontal canal (HC)

	CC	*A A*	*AC*	*BD*	*A C'*	*B'D*
n	65	60	55	55	60	60
$\bar{x}$	25 0±0.8	31.3±0 9	3.2±0.3	3.5±0.3	3 4±0 4	3.5±0 3

Anterior vertical can l (AVC)

	FF'	*HH*	*FH*	*EG*	*F'H'*	*E G*
n	70	65	60	60	60	60
$\bar{x}$	23.2±0 8	28.1±1 0	3 6±0.3	3.5±0 4	3.6±0.4	3.4±0 3

Posterior vertical canal (PVC)

	KK	*FK*		*IJ*	*F'K*	*I'J*
n	70	70		65	0	6.
$\bar{x}$	28.0±1 0	3.1±0.3		3.2±0 3	3.3±0.3	3 0±0.2

Between AVC and PVC

	HK	*H K'*
n	65	65
$\bar{x}$	5 4±0 4	5 4±0.4

responding point on the left as shown in Fig 2 were measured using a sharp needle mounted on the electrode holder of the stereotaxic device Each distance was measured five times within the accuracy of the instru ment that is, 0 1 mm The numerical data are given in Table 2 In four additional skulls the temporal bones were filed down on either hori zontal or vertical plane exposing some of the points shown in Fig 2 The direct measurements confirmed those obtained by dissection of the semi circular canals

The data of Table 2 were used for constructing a geometrical figure which represented the projection of the canals on the horizontal plane As shown in Fig 3 the horizontal canal appeared as a circle while the projection of the vertical canals formed a right angle tangential to the circle For convenience the right angle was completed as a right triangle The values of various segments are given in the table inserted in Fig 3 The values of the angles shown in the figure are the following

$$\varphi_1 = \varphi_2 = 36\ 2 \qquad \varphi_3 = \varphi_4 = 53\ 08 \qquad \varphi_5 = 90$$

The point F in the figure r presented the projection on the horizontal plane of the point where anterior vertical and posterior vertical canals

Fig. 3. Diagram illustrating the projection of the semicircular canals on the horizontal plane. The values of angles through ... are given ... the ... R_h, R_a, R_p are the radii of curvature for the horizontal, anterior vertical and posterior vertical canals respectively. The angle ... subtends the arc of the horizontal canal within the ... vertical ... The values given in the insert were taken from data of Table 2 but the values were rounded off to the nearest integer.

joined forming the common crus (Fig. 4). The distances from various points represented in this figure to the mid-sagittal plane SP can be calculated from Table 2.

B. *Microscopic Measurements*

Histological sections of normal temporal bones were used for measuring the osseous and membranous diameters of each semicircular canal and common crus, and also for measuring cross-section areas of various vestibular structures. From this data the radius and volume of the structures were then calculated.

For measuring the membranous and osseous diameters, serial sections of temporal bones were used. Each section was projected onto a white surface at a magnification of 71 : 1 and diameters measured with a calibrated ruler. The distortion produced by the amplification was so small that no correction factor was used.

The measurements of areas were done in the temporal bones of two cats (A 1371 and B-252) by projecting (71 : 1) upon a cardboard the vestibular area of each section. The outlines of different structures were carefully traced and their area measured with a planimeter. In cat A 1371 one every five sections and in cat B-252, one every ten sections were drawn throughout the temporal bones of both sides. These areas were used for calculating

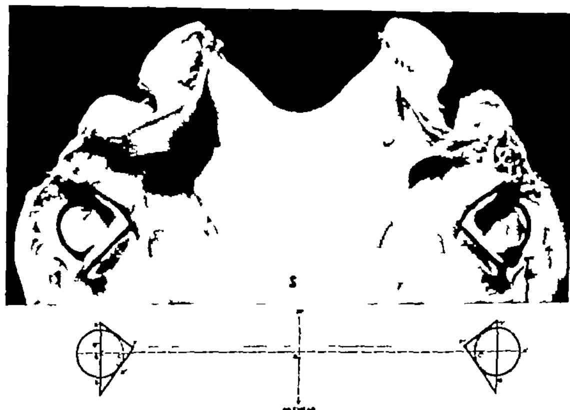


FIG 4 Photograph of exposed semicircular canals seen from above The lower diagram illustrates the projection of the canals on the horizontal plane The values of various segments and angles can be found in Fig. 3 and Table 2 The distances from middle point to the midsagittal plane (SP) can be calculated from Table 2 Direct measurements can be made on the figure by using the scale $s = 10$ mm

the volume of both endolymph and perilymph and the volume of the membraneous tissue forming the maculae and ampullae The calculations were done by means of the trapezoidal rule

$$V = h\left[\tfrac{1}{2}(y_0 + y_n) + \sum_1^{n-1} y\right] \qquad (1)$$

where $y_0, y_1, \ldots, y, \ldots, y_{n-1}, y_n$ are the values of areas measured and h is the thickness of each section times the number of sections between two consecutive measurements The thickness of each section was $20 \times 2 \times 10^{-3}$ cm Since the measurements were made in one every five sections in cat A 1371 and one every ten sections in cat B 2?2 the values of h were 10^{-2} cm and 2×10^{-2} cm respectively We must point out however that the intervals between two successive histological sections used for this purpose were sometimes irregularly spaced This irregularity however does not introduce an important error in the final result

1 *Semicircular canals*

In most sections the contour of either membranous or osseous canal appeared as an ellipse This is due to the direction of the plane of section

TABLE 3 *Diameter d in mm of osseous and membranous semicircular canals*

		Horizontal	Anterior	Posterior
	Number of observations			
Osseous		9		7
	d	0.24 ± 0.01	0.20 ± 0.01	0.27 ± 0.02
Membranous		9		5
	d	0.23 ± 0.01	0.23 ± 0.02	0.21 —

relative to the plane of the canal. Thus, the diameter of both membranous and osseous canal was defined as the smallest value of all measurement made in the right and left temporal bones. The averages of both diameters and their radii were calculated and the result summarized in Table 3. The data showed that in the cat the largest difference between radius of membranous canal and that of osseous canal was about 40 μ (see Fig. 3).

The length of each semicircular canal is important for theoretical considerations. Some investigators consider the canal as a complete ring, others estimate it as one half of a circumference while in fact it is neither one. Actually each canal is an incomplete ring attached to a relatively large cavity, the utriculus. Furthermore the ampullary end of each canal is another relatively large cavity intercalated between the canal proper and *utriculus*. The ampulla is widely open into the utriculus as shown in Fig. 3. Finally the vertical canals are open into another relatively *large cavity* the common crus, intercalated between their non-ampullary *end and the* utriculus. Consequently the length of any semicircular canal is a matter of definition. If we consider it as complete ring, then the length $l = 2\pi R$ (R is the radius of curvature shown in table of Fig. 3). This calculated length was in agreement with that measured *directly by* passing a fine silver wire through the ring formed by the canal and vestibule. The length of the wire was then measured on a ruler. The data *collected* in thirteen pairs of bones (26 direct measurements for each canal) showed that the length of the ring for the horizontal, anterior and posterior canal was 10.6 mm, 11.3 mm and 10.0 mm respectively.

If we assume that each canal is an incomplete ring, then its length L is given by $L = \varphi R$. The values of φ were computed after measuring in each canal the chord L formed by the ends of the incomplete ring. The angle φ subtended by this chord was calculated so that $\varphi = 2\pi - \psi$. The resulting data are given in Table 4. It is perhaps important to point out that in these data, each canal is considered as an incomplete ring of uniform diameter extending from one utricular end to the other.

A third definition is to consider as canal or canal proper that part of the ring excluding the utriculus, ampulla and common crus. Table 5 shows

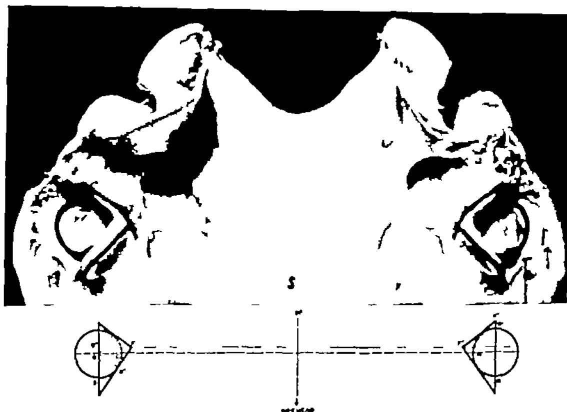


FIG. 4. Photograph of exposed semicircular canals as seen from above. The lower diagram illustrates the projection of the canal on the horizontal plane. The values of various segments and angles can be found in Fig. 3 and Table 2. The distances from indicated points to the mid sagittal plane (SP) can be calculated from Table 2. Direct measurements can be made on the figure by using the scale s = 10 mm.

the volume of both endolymph and perilymph and the volume of the membraneous tissue forming the maculae and ampullae. The calculations were done by means of the *trapezoidal rule*,

$$V = h\left[\tfrac{1}{2}(y_0 + y_n) + \sum_{1}^{n-1} y\right] \qquad (15)$$

where $y_0, y_1, \ldots, y, \ldots, y_{n-1}, y_n$ are the values of areas measured and h is the thickness of each section times the number of sections between two consecutive measurements. The thickness of each section was $20\ \mu = 2 \times 10^{-3}$ cm. Since the measurements were made in one every five sections in cat A 1371 and one every ten sections in cat B 252 the values of h were 10^{-2} cm and 2×10^{-2} cm respectively. We must point out however that the intervals between two successive histological sections used for this purpose were sometimes irregularly spaced. This irregularity however does not introduce an important error in the final result.

1. *Semicircular canals*

In most sections the contour of either membranous or osseous canal appeared as an ellipse. This is due to the direction of the plane of section

Table 4 Biometric data of horizontal anterior and posterior semicircular canals

L_c Chord between ampulla and vestibular end of canal; R radius of curvature; φ = angle subtended by L_c; φ' $2\pi-\varphi$. L = length of canal calculated from equation $L = \varphi' R$. L, L_c and R in mm, φ and φ' in radians.

	Horizontal	Anterior	Posterior
L_c	2.50	2.83	2.17
R	1.70	2.00	1.50
φ	/2	.45π	π/
φ'	3. /2	1.55π	7 /1
L	8.0	9.7	8.0

was 1.83 ± 0.05 mm. The calculated volume of endolymph and perilymph contained in the common crus was 22×10^{-4} cm^3 and 207×10^{-4} cm^3 respectively. A comparison with the volume of the semicircular canal shows that the volume of endolymph in the common crus (22×10^{-4} cm^3) is as large as the total volume of the three canals proper (73×10^{-4} cm^3). Perhaps, the geometry and expansion represented by the common crus may have some effect upon the motion of endolymph in the vertical canals.

3 *Ampulla*

We consider that the ampulla of the semicircular canals can be represented by a semisphere of volumen $V = (^2/_3)\ \pi\ r^3$. From the volume calculated by the trapezoidal rule the cross-section radius r was calculated (Table 9).

A distance of some importance for understanding the mechanics of the cupular motion is the radius of cupula deflection. This "*radius of cupular deflection*" will be the distance from the axis of rotation to the membranous wall of the ampulla. We assumed that the axis of rotation passing along the long axis of the crista is located about its foot as shown in Fig. 8. For

Table 5 Length in mm of the canalicular system

	Utriculus	Ampulla	Canal proper[a]	Common crus	Total[c]
Horizontal	2.2	0.75	7.87		10.6
Anterior	2.2	0.87	6.60	1.83 ± 0.05	11.3
Posterior	2.2	0.81	5.12	1.83 ± 0.05	10.0

[a] Direct measurement on histological sections.
[b] Data from direct measurements on histological sections.
[c] Total length equals length of utriculus, ampulla and common crus.
[d] Mean of 20 samples.
[e] Mean of 25 direct measurements.

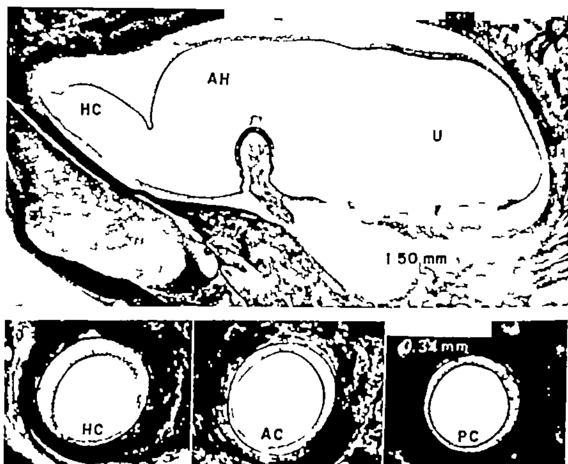


FIG 5 Upper ph t micrograph shows the rel ti n between utriculus (U) and ampulla (AH) f th h ri ontal c n l (HC)
Lower ph t micrograph how a cross-secti n f tl h riz nt l canal (HC) terior erti l canal (AC) nd posterior vertical al (PC) N tice that th mplification for thes ph t mi rograph i different from th t of the upper

the length of each structure as collected from data already given or pre sented later on

The volume of either osseous or membranous canal will depend on our definition The volume of the canal proper was defined as $V = \pi r^2 L$ where r is cross section radius and L length of canal proper The calculated volume for each canal proper is

Horizontal	206×10^{-4} cm³
Anterior	345×10^{-4} cm³
Posterior	232×10^{-4} cm³

2 *Common crus*

The shape of both membranous and osseous walls of the common crus are elliptical The measurements carried out in serial sections of two tem poral bones are presented in Table 6 The length of the common crus was determined from 20 direct measurements on the skull The value obtained

TABLE 6 *Average diameter* $\bar{x}$ *in mm of the short and long axes of the common crus*

n = Number of temporal bones.

	Osseous				Membranous			
	Right		Left		Right		Left	
	Short	Long	Short	Long	Short	Long	Short	Long
n	10	6	10	6	10	6	10	6
$\bar{x}$	0.70±0.07	1.21±0.02	0.69±0.06	1.22±0.06	0.56±0.01	0.95±0.07	0.51±0.01	0.93±0.09

	Average	
	Short	Long
Osseous	0.69	1.23
Membranous	0.55	0.96

5. *Utriculus*

The shape of the utriculus appeared as an elongated body with an elliptical shape in cross-section. The long axis was determined in the serial sections of twelve cats. The number of sections containing the structure times their thickness yielded a length of 2.2 mm. The diameters of the ellipse which appeared in cross-section were measured directly in 16 ears. The averages were 0.835 mm and 1.205 mm for the short and long diameters respectively.

The volume of the utriculus was calculated from the ellipsoid formula ($V = (\ \ )\pi abc$) and from the trapezoidal rule (equation (15)) was 1105 10 cm and 1303 10^{-6} cm respectively. On the assumption that the utriculus was a sphere the radius r and the cross-section area were calculated (see Table 9).

6. *Volume of the labyrinth*

The volume of the vestibule including endolymph, perilymph and soft tissue of sacculus, utriculus and crista were calculated by the trapezoidal

TABLE 7 *Volume of vestibular sense organ in 10 m*

	Endolymph	Perilymph	Soft tissue	Total
Vestibule	1 978	7.665	1 [illegible]	11 [illegible]
Canals	873	318		1 191
Ampulla	1.412	500	511	2 683
Common crus	722	587		1,289
Total	5,215	9 070	2.281	16 566

The volume of the canals is that of the three canal proper

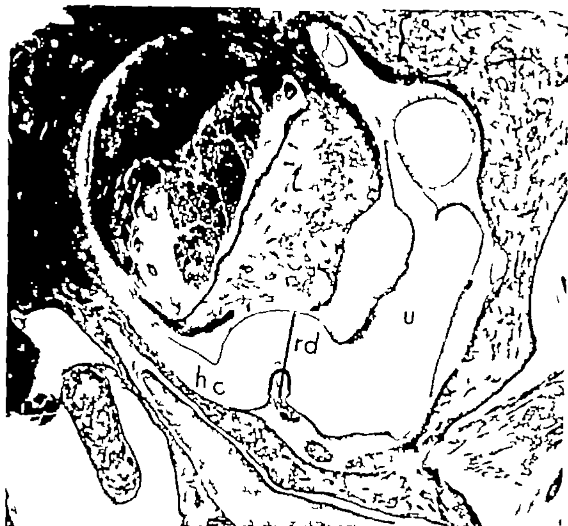


Fig. 6 Photomicrograph of a section passing about the plane of the horizontal canal (*hc*) utriculus (*u*) radius of cupular deflection (*rd*) (0.048 mm)

accurate measurements of this distance it was necessary to process temporal bones so that the plane of section was parallel to the plane of the canal and therefore perpendicular to the long axis of the crista (Fig 6) The measurements showed that the radius of cupular deflection for each canal were the following

Horizontal	0.048 mm
Anterior	0.8[illegible] mm
Posterior	0.030 mm

4 *Sacculus*

The volume of the sacculus as calculated by the trapezoidal rule was 1.016×10^{-4} cm³ On the assumption that the sacculus may be represented as a sphere the radius, *r* and the cross section area were calculated (see Table 9)

data of the vestibular sense organs in our series of animals and in those reported by others, showed a remarkable constancy of their dimensions For instance our measurements regarding the value of r and R are in agreement with those reported by Igara hi (1966) The length f the semi circular canals is a measurement which seems to be at variance among authors. For instance the values given by Wulf (1901) also given by Gray (190) and Camis (1930) for the horizontal anterior and posterior semi circular canals of the cat were mm, 4.5 mm and 4.5 mm respectively These values are close to those given by our definition of canal proper but are quite different from the values given for the canal as an incomplete or complet ring. These discrepancies between investigators is probably due to diff rences in the definition of what i measured a a semicircular canal

The length l of the semicircular canal i included in the calculation of Π as shown in equation (5) Thus, the time constant f the cupula return as defined by equation (12) will show some variation according to what is meant by length of the semicircular canal The variation, however seems to be insignificant If w consider a semicircular canal the incomplete ring by excluding the utriculus, then the time constant t for each canal i the following

Horizontal canal

$$L_1 = \frac{3\pi}{2} R$$

$$\Pi = 12\pi\eta R^1$$

$$\Delta = \pi\mu r^4 R_1$$

$$t = \frac{\Pi}{\Delta_1} = \frac{12\pi\eta R_1^2}{\mu \quad r_1^4} = \frac{12\pi\eta}{\mu} \frac{17}{11} \quad 10^2 \text{ (sec)}.$$

Anterior vertical canal

$$L_2 = 1.55\pi R_p$$

$$\Pi \quad 12.4\pi^2\eta R^1$$

$$\Delta = \pi\mu r^4 R_2$$

$$t = \frac{\Pi}{\Delta} \quad \frac{12.4\pi\eta R_2^2}{\mu \quad r^2} = \frac{12.4\pi\eta}{\mu} \frac{20^2}{15} \times 10^2 \text{ (sec)}$$

Posterio vertical canal

$$L_3 = \frac{\pi}{4} R_3$$

$$\Pi_3 = 14\pi\eta R_3^2$$

$$\Delta_3 = \pi^2\mu r_3^4 R_p$$

$$t_3 = \frac{\Pi_3}{\Delta_3} = \frac{14\pi\eta R_3^2}{\mu \quad r_3^4} = \frac{14\pi\eta}{\mu} \frac{15^2}{12^2} \times 10^2 \text{ (sec)}$$

TABLE 8 *Extrinsic characteristics of the semicircular canals*

	HC	AC	PC
Distance in mm from sagittal plane to			
Center of canal	14 1	12.9	12.9
Outermost point of canal	15 7	14 1	14 1
Innermost point of canal	12.4	11 7	11 7
Angle between canal plane and			
Horizontal plane	0	90	90
Sagittal plane	90	36 52	53 08
Frontal plane	90	53 08	36 52

rule in four temporal bones The averages of this calculation are presented in Table 7 The soft tissue shown in the last column of the table represents the volume of tissue forming the macula of sacculus and utriculus and that of the three cristae ampullares The membranous walls were not calculated because their value is insignificant as compared to that of the sensory epithelium

C Summary of Biophysical Data

In Table 8 some extrinsic metric characteristics of the semicircular canals are summarized The most important intrinsic measurements are presented in Table 9

TABLE 9 *Intrinsic metric characteristics of cat labyrinth*

r = Radius of cross section area R = radius of curvature of canal L = length of the canal circle

	HC canal			AVC canal			PVC canal				
	Osseous	Memb	Ampulla	Osseous	Memb	Ampulla	Osseous	Memb	Ampulla	Sacculus	Utriculus
r (cm)	0 014	0 011	0 061	0 014	0 013	0 058	0 013	0 012	0 069	0 053	0 070
R (cm)	0 17	0 17		0.20	0.20		0 15	0 1			
L (cm)	1 06	1 06		1 13	1 13		1 00	1 00			
Circle area (πR^2) cm	0.09	0.09		0 13	0 13		0 07	0 0			
Cross-section area (πr^2) 10^{-} cm	6.1	3.8	125.	6.3	5.3	106 8	3	4 4	148 6	88.0	151.0
Volume (10^{-4} cm^3)	493	403	546	380	533	400	437	373	608	610	1,363

DISCUSSION

The craniometric data revealed a considerable variation in size of the skull of the so-called young adult cat On the other hand the biometric

TABLE 10 *Endolymph moment of inertia*

ρ = 1.000 (gm/cm³); D = distance from center of semicircul ca l t midsagit l plane; L = length f the anal circle

Canal	r (cm)	R (cm)	L (cm)	D (cm)	$m = \pi r^2 \rho L$ (gm)	Θ $m(R^2 \; \frac{3}{4} r^2)$ (gm cm²)	$\Theta' = \Theta + mD^2$ (gm cm²)
HC	0.011	0.17	1.06	1.41	4.06 10⁻	0.12 10⁻	8.20 10⁻⁴
AVC	0.012	0.20	1.13	1.29	5.60 10⁻⁴	0.22 10⁻⁴	9.70 10⁻⁴
PVC	0.012	0.15	1.00	1.29	4.40 10⁻⁴	0.10 10⁻⁴	7.33 10⁻⁴

11 the values of Π Θ and Π/Θ have been calculated with the assumption that the viscosity of endolymph is like that of water. The corresponding values for the pigeon as given by Money *et al* (1966) are incorporated into this table for comparison. After considering the anatomical differences between cat and pigeon and that the density and viscosity of the cat endolymph is not known yet, the comparison shows consistency of results between the two species. From these observations, we may conclude that the fundamental differential equation f r the canal-cupula endolymph system must be separately applied to each canal in any analytical mechanical study of the labyrinth

Our measurements confirmed the postulate of Jones & Spells (1963) as stated in equation (1) for mammals. The calculation of r (with $n = 0.1818$ and $A = 0.0430$) for our cats with lowest weight (1.7 kg) and highest weight (3.0 kg) was 0.011 cm and 0.012 cm respectively. This is in agreement with the values of r as calculated from measurements presented in Table 3. Similarly the calculated value of R from equation (1) (with $n = 0.1157$ and $A = 2.2160$) gave 0.18 cm and 0.21 cm for the lightest and heaviest cat respectively. This again is in agreement with our measurements presented in Fig 3. Although our results confirmed the observations of Jones & Spell (1963) still the question remains whether their postulate will be consistent with accurate measurements of each canal in a large ariety of species.

TABLE 11 *Values of* Π Θ *and* Π/Θ

Π 16 $\eta\pi^2 R^2$; η η water = 10⁻² (gm/sec cm)

Canal	Cat Π (dynes cm/sec)	Cat Θ (gm cm²)	Cat Π/Θ (sec⁻¹)	Pigeon[a] Π	Pigeon[a] Θ	Pigeon[a] Π/Θ
HC	7.89 10⁻⁴	0.12 10⁻⁴	657	7.8 10⁻	0.21 10⁻⁴	360
AVC	12.62 10⁻⁴	0.22 10⁻⁴	573	28.0 10⁻⁴	1.5 10⁻⁴	190
PVC	5.36 10⁻⁴	0.10 10⁻⁴	536			

[a] Data from Money *et al* (1966)

If the canals are arranged in the decreasing order of R then the relationship t_2 t_1 t_3 can be calculated The results are the following

$$t_2/t_1 = 0.98 \qquad t_1/t_3 = 1.51 \qquad t_2/t_3 = 1.51$$

Therefore if we take the time constant of the semicircular canal with smallest R (posterior vertical canal) as unity then we can write the cupula recovery function (equation (11)) for each canal as follows

$$\text{HC} \quad t_1 = 1.51\, t_3 \text{ (sec)} \qquad \beta_1 = \beta_0 e^{-\frac{t}{1.51}}$$
$$\text{AVC} \quad t_2 = 1.51\, t_3 \text{ (sec)} \qquad \beta_2 = \beta_0 e^{-\frac{t}{1.51}}$$
$$\text{PVC} \quad t_3 = 1.0 \text{ (sec)} \qquad \beta_3 = \beta_0 e^{-t}$$

We would like to point out that these values for the cupula recovery function represent a theoretical approximation based on our measurements of both radii r and R

The graphs of these functions are shown in Fig 7 The derivative of equation (11) for $t = 0$ is

$$\frac{d\beta}{dt} = -\frac{\beta_0}{t} \tag{16}$$

This shows that the tangent at the origin intersects the time axis at the value corresponding to the time constant t

In Table 10 the moment of inertia of the endolymph with respect to the canal center and to the mid sagittal plane has been calculated assuming that the density of the endolymph is equal to that of water It is obvious that the absolute value of these moments of inertia cannot be determined accurately until the density of endolymph in the cat is measured In Table

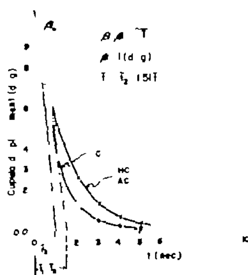


Fig. 7 Function of the cupular return for each canal HC, Horizontal canal AC anterior canal PC, posterior canal

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NYSTAGMUS RATE AS AN INDEX OF CALORIC TEST RESPONSE

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Using a sample of 20 otologically normal adults, the number of nystagmus beats in the period 60 to 90 seconds after the onset of irrigation was found to be a valid measure of caloric test response. This value shows a Gaussian distribution, as does the two-ear difference in this value after logarithmic transformation. Utilising a 10% probability level, less than 33 beats in this period would be abnormal, as would a difference of more than 20 beats between the two ears.

INTRODUCTION

Some otologists use the number of beats over a given period of time as an index of response to vestibular stimulation. The validity of this measure has been questioned.

In a recent report (Hinchcliffe 196 a) evidence was presented to indicate that, of a number of measures of caloric test response, only the maximum velocity of the slow phase of nystagmus induced by an ampullo-petal stimulus (specifically the hot caloric irrigation in the conventional supine position) was a valid measure of vestibular function. Unfortunately in that analysis a measure of nystagmus frequency (beat rate) was not included.

It is the purpose of this paper to assess the validity of nystagmus frequency as an index of vestibular responses to thermal stimulation and to furnish some data on the normal range of measurements. Since the maximum velocity of the slow phase of nystagmus has already been shown to be a valid measure of caloric response, the nystagmus frequency may be cross-validated by determining the correlation existing between these two measures.

PROCEDURE

The caloric test was administered to 20 otologically normal adults with no history of vertigo or other aural symptoms and the induced nystagmus was recorded electro-oculographically. The method of testing was as described in a recent paper (Hinchcliffe 1967 b) with water at 44 C only being used and the subject lying in the conventional supine position. Six

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ZUSAMMENFASSUNG

Eine Untersuchung über die biophysikalischen Dimensionen des Labyrinths der Katze wurde vorgenommen. In jedem Bogengang wurden der Diameter der häutigen und der knochigen Bogengänge und die Radien der Krümmung gemessen. Die Länge und der Umfang der Bogengänge wurden errechnet. Auch der Umfang des Sacculus, Utriculus, der Endolymphe und Perilymphe wurde nach dem Messen ihrer Flächen in histologischen Reihenschnitten errechnet. Die Abstände zwischen den Bogengängen wurden auch gemessen und die Winkel zwischen ihnen bestimmt. Diese Angaben wurden zur Errechnung der Konstante der fundamentalen Differentialgleichung des Cupula-Endolymph-Systems benützt.

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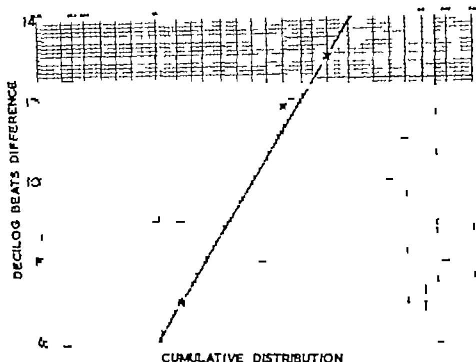


FIG. 2. Cumulati distribution of the difference bet een the tw ears for the mber of ystagmus beat i thi 30-second period. Twenty ot logically normal adults.

on thi type of graph paper) The frequency distributions for the difference in the number of beats between the two ears, although unimodal, was skewed to the left However plotting this data on arithmetical probability paper after a logarithmic transformation indicated that this transformed distribution was Gaussian also (Fig 2) The principal values for the distribution of these measures are shown in Table 1

Tabl 2 shows the correlations that existed between the maximum velocity of the slow phase and the total number of beats in the period 1 min t 1 min 30 sec following onset of irrigation of the ear The table indicates an overall correlation coefficient of about 0 63 which is significant at the p 0 01 le l.

TABLE 1 *Principal value for the distribution of two measures of nystagmus beat rate on 20 otologically normal adults*

Measure	A erage	10 % ile	90 % ile
T tal beats from 60 to 90 sec	54	33	80
T o-ear difference in this total	10	5	20

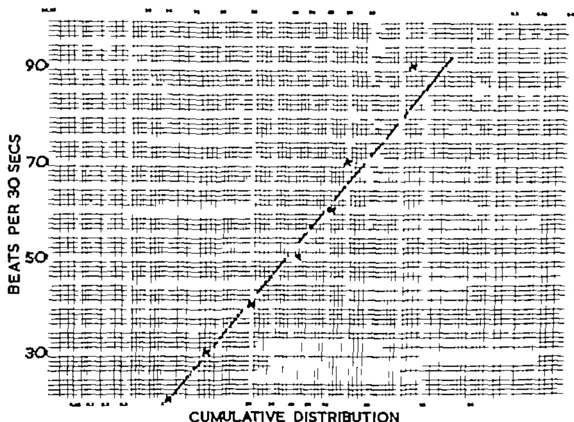


FIG. 1 Cumulative distribution of the number of ny tagmus beats in the period 60 t 90 seconds fte onset of irrigati g an ear with water at 44 C. Dat from a sample of 20 otologically n rmal dults (40 ears)

teen of these subjects were available for retesting and a second caloric test was given to these individuals For this group also a correlation matrix was obtained to determine the correlations existing between the maximum velocity of the slow phase of the induced nystagmus and the number of nystagmus beats in the period 1 min to 1 min 30 sec following the start of irrigation of the ears Correlations were determined for both the right and the left ears separately and for the two occasions of testing

In order to determine the range of values, the frequency distribution of the number of nystagmus beats that occurred in the period 1 min to 1 min 30 sec for each of the 40 ears of the initial samples was examined The frequency distribution of the difference between the two ears in the number of beats over this period was also examined

RESULTS

The total number of beats in the period 1 min to 1 min 30 sec was found to give a unimodal frequency distribution and plotting the data on arithmetical probability paper (Fig 1) indicated that this was a Gaussian distribution (A Gaussian distribution gives a straight line when plotted

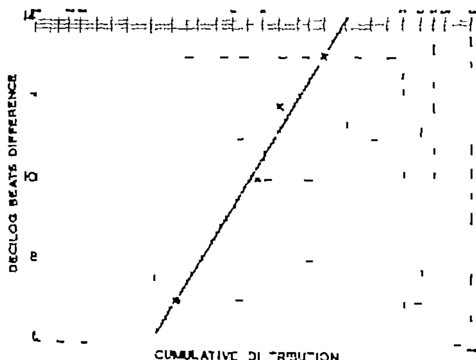


Fig. 2. Cumulative distribution of the difference between the two ears for the number of nystagmus beats in the 30-second period. Twenty otologically normal adults.

on this type of graph paper.) The frequency distributions for the difference in the number of beats between the two ears, although unimodal, was skewed to the left. However, plotting this data on arithmetical probability paper after a logarithmic transformation indicated that this transformed distribution was Gaussian also (Fig. 2). The principal values for the distribution of these measures are shown in Table 1.

Table 2 shows the correlations that existed between the maximum velocity of the slow phase and the total number of beats in the period 1 min to 1 min 30 sec following onset of irrigation of the ear. The table indicates an overall correlation coefficient of about 0.63, which is significant at the $p < 0.01$ level.

TABLE 1. *Principal values for the distribution of two measures of nystagmus beat rate on 20 otologically normal adults*

Measure	Average	10 %ile	90 %ile
Total beats from 60 to 90 sec	56	33	80
Two-ear difference in this total	10	5	20

TABLE 2 *Correlation coefficients calculated for the number of nystagmus beats in the period 60 to 90 seconds after start of ear irrigation and the maximum velocity of the slow phase of the induced nystagmus*

Coefficients are given for right and left ears and test and re-test separately. Sample of 16 otological normal adults.

	Test	
Ear	First	Second
Right	0.71	0.64
Left	0.60	0.62

DISCUSSION

The results (Table 2) indicate that the total number of nystagmus beats counted over the period of 1 min to 1 min 30 sec subsequent to the start of irrigating the ear with water at 44 C with the subject in the supine position is a valid measure of vestibular response, inasmuch as this measure is highly significantly correlated with the maximum velocity of the slow phase of the induced nystagmus.

Until the caloric test can be administered to a random sample of the general population the distributions given in Figs 1 and 2 provide provisional data for ascertaining the normality or otherwise of caloric test records. A composite group of both sexes and various ages was taken because as far as adults are concerned these two variates do not appear to be prominent factors in determining beat frequency.

It is to be noted that nystagmus frequency has an advantage over maximum velocity of the slow phase in the assessment of a caloric response inasmuch as the measurement is the more easily and rapidly determined.

CONCLUSIONS

The number of nystagmus beats occurring in the period 1 min to 1 min 30 sec after irrigation of an ear with water at 44 C for 30 sec and recorded electro-oculographically, is shown to be a valid measure of vestibular response.

Data obtained from normal subjects indicate that if the number of beats in this period and under these conditions is less than 33 or the difference in the number of beats in this period between the two ears is more than 20 then the response is probably abnormal.

ZUSAMMENFASSUNG

Bei 20 Erwachsenen mit normalem Gehör wurde die Anzahl von Nystagmusschlägen während der Zeitspanne von 60–90 sec nach Beginn der Irrigation als ein gültiges Mass bei kalorischer Versuchsreaktion befunden. Dieser Gehalt

zeigt eine Gausssche Verteilung, ebenso wie die 2-Ohr Verschiedenheit in diesem Gehalt nach einer logarithmischen Umbildung. Bei Anwendung eines 10 prozentigen Wahrscheinlichkeitsgrades würden weniger als 33 Pulsschläge während dieser Zeitspanne abnorm sein ebenso wie ein Unterschied von mehr als 20 Pulsschlägen zwischen den beiden Ohren.

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ON THE MIDDLE EAR OF BIRDS

E P GAUDIN

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The structural and functional peculiarities of the middle ear taken from various species of birds have been studied on 80 preparations. The results of a morphological and functional study of the avian middle ear have been compared to the anatomy and physiology of the human ear in its normal status as well as after tympanoplasty An analogous model of the avian tympanic apparatus has been designed

INTRODUCTION

The study of the structure of the avian ear began a long time ago The first publication dates back to the year 1600 (Casserius) One of the first investigations of the avian ear was made by a physician from Riga Wilpert who defended his thesis in 1804 on the theme De differentia organi auditus animalium" Here he states the characteristic features of the structure of the avian ear saying Membrana tympani avium in superficie externa convexa Aves unicum tantum ossiculum proffident " Thus Wilpert had already noted the main peculiarities of the tympanic structure *in birds a tympanic membrane that is external to the outside* like a tent and the existence of a single ossicle, which afterwards was appropriately called a columella—meaning small column

The following authors have similarly investigated the ear of birds Breschet (1836) Huxley (1869) Parker (1869 1879) Wurm (1874) Graff (1885) Hennicke (1889) Gaupp (1898) Suschkin (1899) Smith (1904) Denker (1907) Breuer (1908) Pohlman (1921) Yoshitsune (1924) Dombrowsky (1925 1926) Jellinek (1926) Stellbogen (1930) Wassiljew (1933) Schestakowa (1934 1941) Stresemann (1934) Scheminzky (1935) Wever & Bray (1936) Ibusuki (1938) Brand & Kellog (1939) Granit (1941) Guggenheim (1948) Portmann (1948 1950) Pumphrey (1948, 1960) Prosser Bishop Brown John & Wolff (1950) Buddenbrock (1952) Freye (1952) Freye-Zumpfe (1952) Mazo (1952 1954) Schwartzkopff (1952 1955 1956 1960 1962) Sturkie (1954) Shmalhauzen (1957) Radionova (1958) Kirikae (1960 1963) Vallancien (1963) and Lysuk & Makukha (1966) The most detailed descriptions of the avian ears have been made by Krause (1901)—70 species of birds— and Werner (1960)

This paper was read before th Meeti g f th Est l n Ot l ryng logic Societ T rt (Dorpat) Dec 20-21 1963

The publications of all the above mentioned authors are to be found in periodicals and monographies of different fields, such as the natural sciences, biology ecology zoology paleobiology ornithology and normal and comparative anatomy while in medical literature they are scarce. This makes it difficult for medical researchers to compile a bibliography on this subject. A failure to become acquainted with the available material leads frequently to contradict ry and faulty concepts.

Nearly all the authors tend to characterize the middle ear of birds as a simplified one. Their attention is mainly directed to the fact that the birds possess only one auditory ossicle—th columella—which is situated directly between the tympanic membrane and the oval window.

The ear of birds has attracted attention in otology during the last 10 years in connection with the development of tympanoplasty one basic principle of which i columellization i.e. the concept of a seemingly simpli fied structure of the bird ear. Taking into con ideration the fact that birds and mammals have developed simultaneously and independantly while exi ting in similar acoustical conditions, a comparison of their ears is of xtreme interest from the scientific point of view.

MATERIAL AND METHOD OF EXPLORATION

In order to study the avian ear the anatomical structure and the func tional peculiarities of 80 preparations of several species have been explored (owls—Striges eagle-owls—Bubones *falcons*—Falcones *crows*—Corvi *pigeons*—Columbae *geese*—Anseres *hens*—Galli). Anatomical explora tion of th tympanic cavity were made by means of a binocular magnify ing lens. Some characteristi features were fixed by taking macrophoto- graphs.

Anatomical Explorations of th Birds Middle Ear

It has been shown that birds have a single rod like and relatively long auditory ossiel —columella, its proximal end extending perpendicularly ith a plate called the ellipeolus (a shield) according to the terminology given by Krause (1001). Th ellipeolus is oval. In determining the ize of the columella we were struck by its *length*. The comparative measure ment f th length of the columella nd the longitudinal diameter of the llipeolus in ariou species of bird showed a constant coefficient the column being steadily 3-4 times longer than the longitudinal diameter of th el peclus. That is one of the main differences between the columella f bird and the tapes of mammals. The *height* of the tapes in man i les than twice the length of the longitudinal diameter of its footplate.

Th l peolus is fixed in the oval window by an annular ligament too. An xamination under the microscope has shown thi ligament to be broader t the anterior margin of the ellipeolus. That is why mainly the ibration of the anterior edge are those which are determined when

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probing the clipeolus. This serves as additional proof that the anatomical structure of the avian annular ligament is similar to that of humans

Weber (1960) has pointed out that the columella in birds is lying at an acute angle to the plane of the tympanic ring (ca 30) though he did not attach great importance to this fact The columella approaches the tym panic membran from behind The distal end is attached to the tympanic membrane at the posterior margin That is why the o al window l located behind and out of projection of the tympanic membrane In this respect the ear of birds differs from that of mammals.

The extracolumella i connected by a synchondrosis to the distal end of the columella In young bird the extracolumella is of a cartilaginous structure while in older ones it ha become partly ossified The extra columella has been described by Huxley (1869) although its existence was ignored by otologists when they compared the middle ear of birds to that f man. In fact the extracolumella is an important additional structure in the tympanic apparatus f birds. The extracolumella con ists of three processes—processu extra- supra and infracolumellaris. The biggest of these three is the exterior process continuing in the direction of the colu mella and like the handle of mall u in human is firmly attached to the dorsal radius of the tympanic membrane stretching from its posterior margin toward the centre

In our opinion the essential peculiarities of the extracolumella which should be taken into con iderati n are the f llowing The "end-to-end" connection of the extracolumella to the columella lead to an el ngation of the ystem of the auditory ossicles of birds That such a condition should be established th tympanic membrane in bird protrudes contrary wise toward the external auditory meatus As the tympanic membrane in birds is conically shaped, too an external inspecti n sh ws it t be tent lik

The two remaining processes of the extracolumella pass upwards and downw rd al ng the posterior margin of the tymp nic membrane an choring in it The result i that in bird the auditory ossicles are not con tacting in ne point (as it occurs in mesotympanoplasties) but the tym-panic m mbrane rests on the wh l extracolumella, th shape of which esembles a tripod. Thi peculiarity is important enough to be taken into con ideration, as such junction f the ss icles with the tympanic mem brane accord with the ossicle complex a membrane with a rod Th eardrum f man is con tructed similarly having the function of a conical le (Helmholtz, 1868)

Mo phological Conclusions

When comparing the results recei ed after the anat mical investigation f th middle ear of bird we may point out th following peculiarities as *diff rent* from th structure of the human ear



Fig 1 Columella of th goose ×15

Fig. 2 The oval (1) and round (2) window viewed from the inne ear The ri g h ped band is b oader at the nteri r edg f th ellpeolus 20

Fig 3 The xtracolumella and olum ll of the owl

Fig. 4 The ight tympani t f th goose iewed fr m bel w Th d rsal loc t of th ellpeolus (1) and th incl t f the colum ll toward the t mpani m m bran (2)

Fig. 5 A ide view of the tympanic membrane of the wl

1. The system of the auditory ossicles in birds is lengthened out. As an evolutional necessity it follows that the oval window is dislocated backwards while the tympanic membrane protrudes outwards.

2. The common length of the auditory ossicles is greater than the longitudinal diameter of the clipeolu by 4 to 5 times.

3. The system of the auditory ossicles has an angle of inclination towards the tympanic ring.

Similar features in the avian and human ears

1. The ring-shaped attachment of the clipeolus and the footplate of the stapes are similar in construction enabling vibrations to occur mainly in the anterior part *of the clipeolus and the footplate of the stapes*.

2. The attachment of the auditory ossicle to the tympanic membrane by way of a conical lever (membrane-with-rod) is similarly *shaped*.

Functional Exploration of the Auditory Ossicles of Bird

In the literature we come across the concept that a simplified structure of the avian ear combines with a simple mechanism of its elements in the tympanic cavity. It was believed that the columella transmits the acoustic vibrations of the tympanic membrane to the oval window pistonlike without transforming them in any way. Only Shmalhauzen (1957) and Pumphrey (1960) expressed the opinion that the columella might serve as a specific transformer although they lacked experimental data to prove it.

In order to make a functional study of the auditory system of birds we have explored the mechanism of the displacement of the tympanic membrane and the columella under the influence *of an alternating pressure of* air in the external auditory meatus, considering that the pressure of sound is *a variation of atmospheric pressure*.

For this purpose fresh preparations of the birds' ears were taken, the *tympani* cavities of which were opened from below to examine the columella and the interior surface of the tympanic membrane. A plastic tube was hermetically *attached to the external* auditory meatus and connected with a water manometer. An alternating positive and negative pressure was exerted on the tympanic membrane until a marked displacement by using a microscope took place. The *displacement of* the detailed parts in the tympanic cavity was noted by taking macrophotographs. In each experiment the tympanic cavity was photographed twice in sequence on the same frame with a double exposure during the extreme excursion of the membrane and auditory ossicles, which occurred as a result of the positive and negative pressure in the auditory *meatus* imulating an alternating ec l pres u e

Results of Functional Explorations

It appears that the tympanic membrane oscillates together with the l acol mella and the distal end of the *columella*. As in human the free





Fig 6 The interior vi w f the tympanic m mbra e with xtracolum lla nd columella of the g ose

Fig 7 Ext em excursion f th colum lla (goose) The right r vi wed from below Oscillati n f th colum ll in cross directi n (by d ubl e positi n)



Fig 8. The exterior iew of the t mpa ic membra f the cock. Proces u e tra columell ris is ituated t the d rsal part f the t mpa ic m mbrane

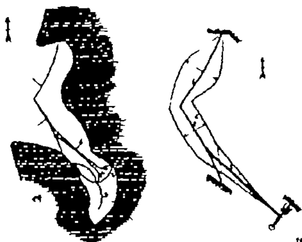


Fig. 9. A schematic view of the tympanic system of the right avian ear from below (1) External auditory meatus; (2) tympanic cavity (3) tympanic membrane (interior part); (4) columella; (5) extracolumella (6) lipeolus (on l al don); (7) round window (8) cochlea; (9) membrana basillaris.

Fig. 10. Mechanical (kinetic) analogous model of the tympanic system of birds. (A) Position of silence (B) position of extreme external dislocation; (C) position of extreme internal dislocation. (1) Tympanic membrane; (2) extracolumella; (3) columella; (4) clipeolus.

shuttle back and forth the inert perilymph in the scalae Thus it is clear why an elongation of the auditory ossicles has taken place during the phylogenesis of birds.

It is interesting to note that in the analogous vectorial model of the human tympanic system (Gandin, 1967) the auditory ossicles have the same specific weight in the correlation of the parameters of acoustic vibrations in matching the two systems.

ZUSAMMENFASSUNG

Das Mittelohr der Vögel ist vom Standpunkt des anatomischen Aufbaus wie auch des Funktionsmechanismus eigenartig, und seine Anatomie und Physiologie unterscheidet sich vom menschlichen Ohr. Was den Koeffizienten der Transformationswirksamkeit der akustischen Vibrationen betrifft, so bleibt das Vogelohr dem menschlichen Ohr nicht nach. Daraus folgt, dass die Annahme von dem vereinfachten Aufbau und der Funktion des Vogelohres unbegründet ist. Dieser Annahme lag der sogenannte „columella effect" zugrunde bei Rekonstruktionschirurgie des Mittelohrs zur Erklärung der morphologischen Analogismen nach solchen Operationen und zur Rechtfertigung einiger tympanoplastischen Verfahren die nicht experimentell bestätigt worden waren. Doch nach Operationen denen der „columella effect" zugrunde gelegt wurde, ist keiner der erwähnten Merkmale des Aufbaus und der Funktion des Mittelohrs der Vögel in den neotympanalen Systemen beim Menschen vorhanden.

(anterior) part of the tympanic membrane receives the greatest displacement Because of the sloping position of the columella towards the tympanic membrane its vibrations are transmitted by the column not longitudinally but in a transversal side excursion which occurs across the position of silence

Therefore it is quite natural that the clipeolus does not oscillate symmetrically and pistonwise hence the anterior edge is mainly displaced Thus the vibrations of the clipeolus in birds, figuratively expressed remind us of the movements of a musician s foot tapping as it rests on the heel According to the investigations by Buck (1870) Wrightson & Keith (1918) Fumagalli (1949) and Wanderer (1953) similar asymmetric vibrations also occur in the footplate of the human stapes as a result of the function of the malleus and incus which act as levers

Functional Conclusions

A comparison of the physiological peculiarities of the middle ears in birds and humans makes it possible to remark on their differences and *similarities The main difference is in the character of the vibrations of* the columella in birds which differs from the vibrations of the stapes after mesotympanoplasty when the so-called columella effect is produced

A similarity between the mechanism of the middle ear of birds and humans can be detected when a comparison is made of the function of the tympanic membrane and by observing the specific displacements of the columella and the stapes, i e their side vibrations with "pedalling" of the clipeolus and the footplate of stapes

An Analogous Model of the Avian Tympanal System

Based on experimental observations of the function of the elements in the tympanic cavity and considering the anatomical peculiarities of the structure of the birds ear we have designed an analogous model of the middle ear of birds In this model the position of silence (A) and the extreme displacements of the tympanic membrane and the auditory ossicles during vibrations (B C) have been presented

It appears that on the whole the auditory ossicles work as a lever with two arms The long arm is the column and the external process of the extracolumella The short arm is represented by the longitudinal diameter of the clipeolus. Hypomochlion corresponds to the posterior edge of the clipeolus.

As in the ear of bird the long arm of the lever is 4–5 times longer than the short one and the amplitude of vibrations of the extracolumella is decreased by as many times compared to the vibrations of the anterior margin of the clipeolus The pressure of sound increases accordingly to overcome the acoustic impedance of the air liquid boundary in order to

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DIE MIKROPRÄPARATION DER COCHLEA

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Genaue Beschreibung der Mikropräparationstechnik der Cochlea. Sie ermöglicht eine exakte und rasche Darstellung des Cortischen Organs, des Ligamentum spirale mit Stria vascularis sowie des Ganglion spirale und deren Veränderungen, wobei ein Cytocochleogramm die Auswertung der morphologischen Befunde statistisch sichert. Daneben lassen sich mit dieser Technik bei Gefrierpräparation kleinste Peri- und Endolymphportionen gewinnen. Die Mikropräparation stellt so eine wichtige Methode zur Untersuchung der Cochlea dar.

Morphologische und biochemische Untersuchungen an den Strukturen der Cochlea — sei es, um Auskunft über physiologische oder über pathologische Vorgänge zu erhalten — haben letztlich das Ziel, Relationen aufzuzeigen, die sich später einmal für die Klinik, für die Behandlung unserer Patienten verwerten lassen. Dabei erfordert die Mannigfaltigkeit der Strukturen, die zahlreichen zu untersuchenden metabolischen Vorgänge eine Vielzahl verschiedener Methoden. Von diesen bevorzugen wir seit langem zur Darstellung der häutigen Cochlea die Mikropräparationstechnik. Sie ist gewebsschonend und gibt die Möglichkeit, sich rasch über den jeweiligen Status zu orientieren.

Die Mikropräparation der Cochlea wurde zum ersten Mal von Neubert (1950) angegeben. Wir üben dieses Verfahren modifiziert und erweitert seit 1954. Auf ihm basieren unser Cytocochleogramm, das die statistische Sicherung der morphologischen Befunde ermöglicht, sowie unsere Gefrierpräparation der Schnecke zur Gewinnung kleinster Peri- und Endolymphportionen. Die Technik der Mikropräparation ist bisher nirgends klar und verständlich publiziert. Da wir diese Methode aber für ein wichtiges Verfahren zur Untersuchung der Strukturen des Innenohres ansehen, halten wir es für notwendig und gerechtfertigt, unsere langjährige präparatorische Erfahrung zusammenfassend darzulegen. Sie wurde vorwiegend an der Cochlea des Meerschweinchens, daneben auch an der des Kaninchens, der Katze und des Menschen gewonnen.

A. *Mikropräparation der Cochlea*

1. *Cortisches Organ*

Das günstige Körpergewicht für Meerschweinchen, deren Cochlea mikropräpariert werden soll, beträgt etwa 200 g. Die Tiere werden sofort nach Versuchsende mit dem Amputationsmesser oder, bei kleineren Tieren, mit einem Scherenschlag getötet. Vom Foramen occipitale magnum aus lassen

sich beide Schnecken mit der Schere in 1–2 Minuten aus dem Schädel herauslösen und in die Fixationslösung einbringen. Luftblasen werden aus der eröffneten Bulla sorgfältig entfernt. Zur Fixation — sie erfolgt bei Zimmertemperatur — hat sich bei uns die Bouinsche Lösung, die jedesmal frisch angesetzt werden muß, am besten bewährt. Nach 24 Stunden werden die Schnecken aus der Fixationsflüssigkeit herausgenommen und in 70%igem Alkohol ausgewaschen. Versuche mit supravitaler Fixation ergaben keine besseren morphologischen Bilder.

Zunächst werden die die Bulla umgebenden Weichteile sowie die knöchernen Wände mit der Schere so weit entfernt, daß die Cochlea noch gut zwischen Daumen und Zeigefinger gehalten werden kann. Falls einmal dabei die Schnecke zu sehr aus dem Felsenbein herausgesprengt werden sollte, läßt sie sich leicht auf einem kleinen Gipsblock befestigen. Wir halten es für wichtig, daß die Cochlea während des ganzen Präparationsvorganges in der Hand gehalten wird und nirgends fest fixiert ist. Denn nur durch die uneingeschränkte Bewegungsmöglichkeit ist ein optimales Arbeiten gewährleistet. Zu Beginn der Präparation fräsen wir unter der Präparierlupe bei 10facher Vergrößerung mit einem feinen Rosenbohrer die knöcherne Leiste an der Hinterwand ab, mit der die Cochlea mit dem Felsenbein in Verbindung steht. Anschließend wird mit dem Finierer die Knochenkapsel der medialen Wand so weit abgeschliffen, daß das Ligamentum spirale in allen Windungen durchschimmert. Ein Abschleifen der lateralen Schneckenkapsel ist nach unseren Erfahrungen nicht erforderlich, denn sie stellt nur eine dünne, leicht abzulösende Lamelle dar.

Für den weiteren Verlauf der Mikropräparation sind nun Vergrößerungen 25- und 50fach zweckmäßig. Nach Abschieben der restlichen, die Schnecke deckenden Mittelohrschleimhaut wird zunächst an der Schneckenspitze ein kleines Loch mit einem feinen Häkchen eingebrochen (Abb. 1). Von dieser Lücke aus erfolgt dann mit dem Häkchen das Ablösen des dünnen Knochens über dem Ligamentum spirale, so daß dieses zur Darstellung kommt (Abb. 2). Dabei ist es sinnvoll, die geronnene Lymphe auszuspülen und die Schnecke mit Hämatoxilin oder mit Methylenblau leicht anzufärben. Die Strukturen werden dadurch im Detail deutlicher sichtbar.

Die Präparation erfolgt also von der Spitze her, wobei wir bestrebt sind, den Modiolus stehenzulassen. Nach Abtragen der knöchernen Kapsel stellt sich das Ligamentum spirale dar und wird, ebenso wie die als zarte Netzstruktur erkennbare Reißnersche Membran, mit einer feinen Lanzette abgenommen. Noch besser als eine angeschliffene Lanzette haben sich zur Präparation der häutigen Teile kleine Rasierklingensplitter, z. B. in feinen Gefäßklammern fixiert, bewährt. Diese Splitter öfters erneuert, lassen eine sehr sorgfältige und saubere Präparation zu. Nun wird die Membrana tectoria vom Cortischen Organ abgehoben, und vor uns liegt die Basilarmembran mit dem Cortischen Organ (Abb. 3). Sie wird vom Modiolus abgetrennt und in Stücke geteilt, die jeweils $^1/_3$–$^1/_2$ Schneckenwindung entsprechen. Dieses Unterteilen des Cortischen Organs erfolgt immer am

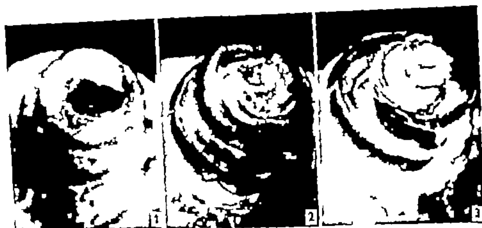


Abb. 1. Beginn der Mikropräparation der Cochlea. Ein Stückchen de knöchernen Schneckenkapsel ist entfernt und da Ligamentum piral der 4 Wind ng ben sichtbar

Abb. 2. W iterer Schritt der Mikropräparation. Nach Entfernung der Kapsel der Cochlea liegt das Ligamentum pirale der Spitzenwindung frei. Der dunkle Streifen nt pricht der pigmentreichen Stri ascularis.

Abb. 3. Basilarmembran der 4 Schnecken indung nach Entfern g des Ligament m spirale. Ein kleines Stück am Übergang der 3. zu 4. Windung ist bereits entfernt.

Ganzpräparat und nicht isoliert in Flüssigkeit Jedes Stückchen der Basilar membran wird nun in ein vorbereitetes und numeriertes Töpfchen mit Farblösung eingelegt.

Neben unserem Präparationsmikroskop liegt stets ein Schneckenschema, getrennt für die rechte und linke Seite. In dieses Schema wird die Topographie aller abgetrennten Teile sorgfältig eingetragen, um die spätere Auswertung zu erleichtern. Ebenso werden auch eventuelle Beschädigungen der Basilarmembran hier vermerkt. Auf diese Weise wird Windung für Windung präpariert und registriert. Am Ende steht nur noch der Modiolus. Aus ihm läßt sich nun das Ganglion spirale isolieren

2. *Ganglion pirale*

Nach der Präparation des Cortischen Organs steht nur noch die Schnek kenspind l mit der *Lamina spiralis ossea sowie Teile der knöchernen* Zwischenwände, welche die einzelnen Windungen voneinander trennen. Die letzteren werden entfernt, so daß sich nur noch die Lamina spiralis ossea um den Modiolus windet. Diese wird durch die Fissura spiralis in 2 Blätter geteilt, wobei das obere vestibuläre recht dick das untere, tym panale nur dünn ist. Weiter zur Schneckenachse hin liegt das Ganglion spirale im Rosenthalschen Kanal, einem Hohlraum, der durch das Auseinanderweich n der beiden knöchernen Blätter gebildet wird. Beginnend an der Spitze des Modiolus wird nun mit einer feinen Lanzette in die Fissura spiralis ingegangen und d r Knochen vorsichtig in kleinen Stück



Abb 4 Stadi n der Mikropräparation des Ganglion spiral 1 Mitt ls iner feinen Lanzette Abbrechen der beren Knochenlam lle des Rosenthalschen Kanals, die bei 2 schon teilweise ntfernt ist 3. Nach völlig m Abtrag n des oberen Blattes folgt die Wegnahme des unt ren. 4 Herausnahme des Gangli nwulstes. Di gestrichelte Li ie zeigt die Abtrennst lle von den Fasern des N cochlearis an

chen abgebrochen (Abb 4) Zweckmäßig beginnt man dabei zunächst mit der Entfernung des oberen Blattes und präpariert dann die dünne Knochen lamelle unterhalb ab Um Artefacte zu vermeiden muß die Spitze der Lanzette beim Abbrechen beider Blätter immer am Knochen bleiben wodurch ein Eindringen in das Nervengewebe verhindert wird

Nach Entfernen des Knochens liegt das Ganglion frei und stellt einen dicken Wulst dar der sich spiralig um den Modiolus windet. Der Wulst hängt nur noch an den zum N cochlearis ziehenden Fasern Diese werden sorgfältig durchtrennt und das Ganglion wird herausgenommen wobei es wegen der Brüchigkeit des Gewebes selten gelingt mehr als eine halbe Windung zusammenhängend zu entfernen Da die Windungen des Gang lion im Vergleich zu denen der Basilarmembran wesentlich enger sind ist ein solches Ganglionstück verhältnismäßig klein.

Die Mikropraparation der Cochlea anderer Säugetiere und auch der des Menschen wird im Prinzip auf gleiche Weise durchgeführt Da aber die Schnecke bei vielen ahnlich wie beim Menschen im Felsenbein eingebettet liegt muß die Entnahme der Cochlea bzw des Felsenbeins aus dem Scha del den anatomischen Relationen angepaßt werden Bei der Präparation selbst ist ein Vielfaches an Zeit erforderlich da das Abfrasen der dicken Knochenlage die die häutige Cochlea umgibt sehr langwierig ist Die Weichteilpräparation erfordert dann keinerlei besondere technische Kniffe mehr

3 *Histologische Bearbeitung*

Die mikropräparatorisch gewonnenen Stücke der Basilarmembran kön nen nun den einzelnen Färbungen ahnlich wie Gefrierschnitte unterzogen werden (Selbstverständlich ist es auch moglich die ganze Schnecke nach abgeschlossener Fixation zunächst zu färben und dann die Praparation anzuschließen) Jedes numerierte Basilarmembranteilchen muß dabei fur sich bearbeitet werden Auf Grund der geringen Größe und der Empfind lichkeit der Präparate ist zu ihrer Schonung zu empfehlen diese in Hohl

schliff-Objektträger zu bringen und mit einer feinen Pipette die Lösungen zuzugeben bzw. abzusaugen, so daß die Gewebsstücke nicht immer wieder berührt werden müssen. Nach Beendigung des Färbeprozesses erfolgt die Entwässerung in aufsteigender Alkoholreihe bis zum 96%igen Alkohol. Von dort werden die Stücke in Terpineol gebracht. Diese Lösung macht die Stücke geschmeidig, hellt sie auf und verhindert eine Schrumpfung, so daß genügend Zeit bleibt, die Präparate vor dem Eindecken seitenrichtig und eben auf dem Objektträger auszubreiten. Xylol haben wir wegen der Schrumpfungsgefahr vermieden.

Die Stücke des Ligamentum spirale sowie die des Ganglion spirale sind im Gegensatz zu den Sektoren der Basilarmembran relativ dick und zeigen einen wenig geordneten Aufbau, so daß eine Verwertung als Ganzpräparat wenig sinnvoll ist. Die einzelnen Zellen überlagern sich dabei derart, daß die feineren Strukturen und deren Veränderungen nicht sichtbar werden. Wir haben deshalb die Präparate stets eingebettet und in dünne Schnitte geschnitten.

B. Das Cytocochleogramm

Schon bei unseren ersten Beschallungsversuchen hatten wir begonnen, die gesamte Cochlea durchzumikroskopieren, die Zahl der Kerne in der Relation normal : geschädigt auszuzählen und sie in Schneckenschemata einzutragen (Beck, 1953, 1956). Eine exakte statistische Auswertung erfolgte jedoch damals noch nicht. Auf Anregung von Terayama verwenden wir nun für die statistische Auswertung seit längerem folgendes Prinzip:

In das vorher bezeichnete Schneckenschema werden 24 Zählpunkte markiert (Abb. 5). Da nun jedes Basilarmembranstückchen in das Schema genau eingezeichnet wurde, läßt sich jeder Zählpunkt auf dem mikroskopischen Präparat ebenfalls genau bestimmen. Die Lage des runden Fensters dient dabei als Bezugspunkt. Bei der mikroskopischen Auswertung werden zu jedem Zählpunkt mindestens 100, meistens 200 Zellen ausgezählt. Aus dieser Zahl wird der Prozentsatz der veränderten zu den unveränderten Zellen bestimmt und in die darunterliegende Tabelle sofort eingetragen. So lassen sich innere und äußere Haarzellen getrennt voneinander auswerten, ebenso wie Schwellkerne, Kernpyknosen, Plasmaveränderungen und ähnliches. Die gewonnenen Zahlen werden statistisch ausgewertet und in Kurven dargestellt (Abb. 6). Das auf diese Weise entstandene Cytocochleogramm der Schnecke erlaubt jetzt eine genaue statistische Auswertung und so eine Korrelation der morphologischen mit anderen, z. B. elektrophysiologischen Untersuchungsmethoden.

C. Gewinnung der Innenohrflüssigkeiten

Mit Ausweitung unserer Experimente trat zwangsläufig die Frage auf: wie verhält sich die Innenohrflüssigkeit nach akustischer Belastung oder nach Einwirkung ototoxischer Pharmaka. Da uns bislang vor allem der

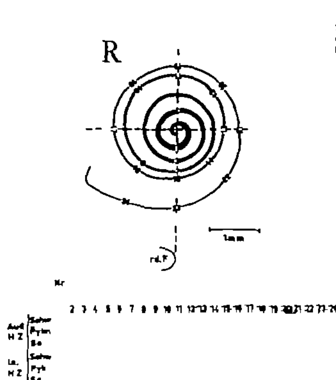


Abb. 5.

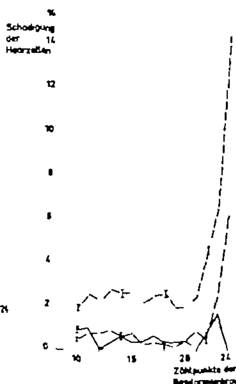


Abb. 6

Abb. 5 Formblatt des Cytocochl ogramms. Im oberen Schema wird di genaue Lage der ntn mmenen *Häutchenpräparate ei gezeichnet, in das unt re werd n di Prozentzahl* n d veränd rt n Ha rz llen in den inzeln n Zählpunkt n ing tragen. Di Auswertung erf lgt getrennt nach äußeren Haarzell n (*Ä ß H Z*) inneren Haarzellen (*In H Z*) Gewertet w d n Schwellkerne (*Schw*) Kernpyknosen (*Pykn*) und die S mme beider W rt (*Sa.*)

Abb. 6 Bei pi l ine statistischen Au wertung mo phol gische Veränderungen im Cortischen Organ. Jed Kurve zeigt den Durchschnittswert v n 10 Meerschw inch n *Ordinate* Zählpunkte uf der Basilarm mbran (gl Abb. 5) *Abs.iss* Prozentzahl der *geschädigt n Z llen.* ——— *Kontrolltiere* ---- *Tiere, die 10 T ge 250 mg Str pto-*mycin-Sulf t pro die L m erhalt n hatt n - - - gleiche Streptomy inm ge gelö t in Ozothin® st tt in qua d st.

Eiweiß- und Ribonucleinsäurestoffwechsel interessiert hatte erschien es am sinnvollsten das Verhalten der Eiweiße auch in den Lymphen zu über prüfen Zur Untersuchung kleinster Lymphproben war dabei die immuno-elektrophoretische Darstellung, für ihre Gewinnung die Gefrier Praparation am zweckmäßigsten (Beck & Holz, 1965) Da uns eine Kühlkammer nicht zur Verfügung stand haben wir folgenden Weg gewählt (Holz, 1964)

Die aus dem Schädel herausgelösten Schnecken der Meerschweinchen wurden sofort in flüssiger Luft eingefroren und auf einem Mikrotom mon tiert Mit Hilfe eines von uns selbst gebauten Kryostaten läßt sich die Temperatur der Schnecke auf −10 halten so daß unter 25- bis 30facher Vergrößerung ohne Gefahr des Auftauens die Schnecke präpariert werden kann Mit zugeschliffenen Zahnsonden wird zunächst ähnlich wie oben für die Häutchenpräparation dargestellt der Knochen entfernt (Abb 7 *a*) Darunter liegen die gefrorenen häutigen Strukturen der Cochlea sowie die



Abb. 7 Gefrierpräparation der Cochlea. a. Beginn der Präparation. Schnecke g froren. b Ei Stück der Knochenkapsel de Basal indung ist entfernt. Dar ter ind die g frorene Perilymphe (1) nd das Ligamentum spirale (2) ichtbar

gefrorenen Lymphen (Abb. 7 *b*) Gewebe und Lymphen können dabei gut voneinander isoliert werden. Erkennt man als Folge der Dekapitation Blut beimengungen in der Lymphe, so wird die Schnecke sofort aus dem Ver such genommen Ohne Zeitnot und unter relativ guter Sicht lassen sich etwa 2 l Perilymph in Form kleinster Gefrierstückchen mit der Lanzette u der Basalwindung gewinn n Um genügend große Mengen von Endolymphe für die Immuno-Elektrophorese zu erhalten sind Sammelproben au erschiedenen Windungen notwendig. Die gefrorenen Lymphportionen werden nach Entnahme sofort auf die für die Immuno-Elektrophorese vor bereit ten Objektträger gebracht

Da Gehäuse des selbstgebauten Kryostaten (Abb. 8) stellt ein gut isolierter Karton dar An den Seiten finden sich 2 o ale Öffnungen für die Hände Außenmaße des Karton 41 41 41 cm Innenraum 20 × 12 × 10 m

Au dem abnehmbaren Deckel wurd ein Loch mit einem Du chm sser 14 cm hera isgeschnitten, so daß ein genügend große Beobachtungsluck fur di Präparierlupe orhanden war Zum Schutz gegen Wärme ein trahlung wu d die Öffnung mit inem Doppelfenster us einf chem Gla erschlossen D e Lupe befindet sich, fi iert an inem Stativ ußer halb des gekühlten Raumes und ihr Objektiv sitzt 1 m Fen ter auf Auf d m Bod n des Kart n sorgte ein m t flüs igem Stickstoff gefülltes Lit r Dewar-Gefäß für di nolig Kühlung. Das Dewa -Gefäß rhielt einen eisernen Deck l, dessen Bohrung len Sockel mit de aufgefrorenen

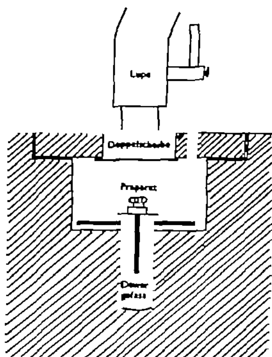


Abb. 8 Schematische Darstellung des selbstgebauten Kryostaten zur Gefrierpräparation.

Schnecke aufnehmen konnte Der Metalldeckel hatte einen angeschweißten Eisenstab der in den flüssigen Stickstoff tauchte und so die durch die Mikroskopleuchte entstandene Wärme ausreichend ableitete Die Temperatur betrug bei dieser Anordnung – 6 unmittelbar auf dem Block unter – 10 bei normaler Raumtemperatur Lederhandschuhe schützen die Hände vor Kälteschäden Der Abstand Lupe–Objekt richtete sich nach dem Arbeitsabstand der verwendeten Präparierlupe

Die immuno-elektrophoretische Aufschlüsselung der Lymphproben erfolgte auf dem kleinen LKB Gerät nach der üblichen Methode (Einzelheiten s bei Beck & Holz, 1960) Zu bemerken ist, daß wir mit käuflichen Antisera zunächst keine guten Erfahrungen machten und dazu übergegangen sind eigene Antisera herzustellen Als Tierspezies für das Anti Meerschweinchenserum eignete sich dabei das Kaninchen besser als die Ratte Nach etwa 4–6 wöchentlicher Sensibilisierung der Kaninchen ließen sich gute Meerschweinchen Antiserum Titer nachweisen die erheblich höher waren als diejenigen der käuflichen Sera.

DISKUSSION

Seit 1954 wird von uns an der Cochlea die Mikropräparationstechnik durchgeführt. Sie hat sich im Laufe der Jahre ständig erweitert und verbessert für morphologische und modifiziert auch für biochemische Untersuchungen bestens bewährt Wir haben deshalb jetzt die technischen Details, die bislang nirgends eingehend beschrieben sind auf Grund un

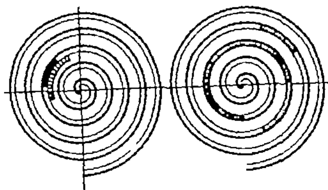


Abb. 9. Abb. 10.

Abb. 9. Lage und Ausdehnung des ergriffenen Sektors der Basilarmembran nach Sinustonbeschallung 500 Hz und (□□□) 80 dB bzw. (■■■) 90 dB. Beschallungsdauer 2 mal 30 sec

Abb. 10. Ausdehnung der Zellveränderungen (der Basilarmembran nach einer Beschallung mit 500 Hz, 110 dB, 1 mal 40 sec beim Meerschweinchen, das sehr empfindlich gegen Tonbelastung ... Das kleine Areal im mittleren Drittel der 2. Windung zeigt die Lokalisation der metabolischen Veränderungen, die durch die aural harmonics zustande sind. (Hier die 2. Harmonische bei 1000 Hz.)

serer Erfahrungen zusammenfassend dargestellt. Die Methode hat neben der Gewebsschonung den Vorteil, daß die Ergebnisse rasch vorliegen und auch rasch eine statistisch gesicherte Auswertung der morphologischen Befunde möglich ist.

Eine statistische Auswertung von Veränderungen der Cochlea wird von uns schon seit langem vorgenommen (Beck, 1955, 1956) und wir legten bei der morphologischen Untersuchung immer besonderen Wert darauf, daß stets die ganze Schnecke erfaßt wurde. Die Notwendigkeit der Untersuchung der ganzen Cochlea zeigt z. B. Abb. 9, auf der die Areale der Basilarmembran eingetragen sind, die nach einer Tonbelastung mit 500 Hz metabolische Veränderungen zeigten. Diese Abschnitte konnten nur durch Präparation auch der dem Felsenbein anhaftenden Seite der Cochlea aufgedeckt werden. Noch deutlicher zeigt sich diese Notwendigkeit der Bearbeitung der ganzen Cochlea in Abb. 10, auf der die von uns 1960 aufgezeigten morphologischen Veränderungen des Cortischen Organs im Bereich der Harmonischen bei intensiver Tonbelastung mit 500 Hz eingetragen sind. Sie ließen sich nur durch die Bearbeitung der ganzen Basilarmembran nachweisen. Eine Auswahl des zur Untersuchung und Auswertung kommenden Areals der Cochlea z. B. aus präparatorisch-technischen Gründen – erfahrungsgemäß ist ja die in die Bulla hineinragende Seite der Cochlea am leichtesten zu präparieren — kann so niemals den Anforderungen einer exakten morphologischen Untersuchung gerecht werden.

Aus dieser Erfahrung und den Forderungen, exakte statistische Daten

zur Korrelation verschiedener Untersuchungsmethoden der Cochlea zu erhalten (Stange *et al* 1966) entstand unser Cytocochleogramm das die detaillierte statistische Auswertung der Zellen des Cortischen Organs und ihrer Veranderungen gestattet Wir haben so die Möglichkeit rasch die Ergebnisse verschiedener Untersuchungsmethoden zu korrelieren und damit umfassendere Aussagen uber die Funktion der Cochlea zu erhalten Die Mikropräparation gestattet weiter eine einwandfreie Gewinnung von Labyrinthliquor Die Präparationstechnik muß dabei zwar etwas variiert werden doch ist dies bei Kenntnis der Grundprincipien der Mikropräparation ohne Schwierigkeiten moglich Auf Grund unserer Erfahrungen halten wir so die Mikropräparation für eine äußerst wichtige Methode zur Untersuchung der Cochlea bzw des gesamten Innenohres

SUMMARY

Exact description of the micropreparation of the cochlea It allows an exact and quick representation of the organ of Corti, the spiral ligament with the stria and the spiral ganglion and their morphological variations. A cytocochleogram guarantees the statistical interpretation of the morphological results. Further it is possible to gain very small portions of perilymph and endolymph with this technique Thus the micropreparation represents a very important method in investigating the cochlea

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LOSS OF HEARING FOLLOWING THE SYNDROME OF VAN DER HOEVE-DE KLEYN

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Osteogenesis imperfecta, often called the syndrome of Van der Hoeve–de Kleyn consists of blue sclerae fragilitas ossium and hardness of hearing. Previous authors have considered the impairment of hearing to be due to and identical with, otosclerosis. But in recent years some authors have questioned this opinion. The author presents four cases in which a stapes mobilization was performed in five ears.

The combination of the symptoms, *blue sclerae osseous fragility* and impaired hearing, is well known According to Bigler (1923) it was first mentioned in 1022 by Dighton—and a little later (1917) by Bronson as well as by Fraser

The combination is nevertheless often called "Van der Hoeve–de Kleyn's syndrome" *after a publication (1918) in which the authors describe* two Dutch families. In these familes they detected one or several of the above mentioned symptoms in a *large* number of *the families* members.

Later the syndrome has been discussed by several authors Ruttin (1922) Nager (1922) Bigler (1923) Gimplinger (1926) Brickley (1941) Fowler (1949) Lindsay (1950) Bryan *et al* (1956) and Sooy (1960)

It is also mentioned in textbooks Jackson & Jackson, *Diseases of the Nose Throat and Ear* (1945) Nylén, Andersen, Leegaard & Siirala, *Nordisk Lærebok i Oto-Rhino-Laryngology* (1958) and Coates, Schenk & Miller *Oto-Laryngology* (1960)

In Scandinavian literature there are communications by Felnes (1949) Hernberg (1952) Berfenstam and Smårs (1956) and Herberts *et al* (1963)

According to Bigler both Bronson and Fraser considered the impairment of hearing in cases of blue scleras and osseous fragility to be due to otosclerosis. The same *opinion is held by Van der Hoeve–de Kleyn and by* the majority of later authors.

The basis for this opinion appears to be limited to purely clinical data. In the first place the nature of the impairment of hearing is found by the majority to be mechanical (conductive)

Histological observations of localized osseous changes in the area around the foramen ovale, as seen in otosclerosis, have been made in only 2 cases according to the available literature (Ruttin, 1922 *Ogilvie, 1920*)

It is postulated, however lately by Simson-Hall & Ogilvie, that the histological picture in osteogenesis *imperfecta and otosclerosis* generally has so

many traits in common, especially concerning the osteoblasts, that this must be an expression of a common etiology'

Altmann opposes this and emphatically declares that there is no support for this assumption of a common basic etiology in the available histological data

Nager is also said to have found otosclerotic changes in the temporal bone from patients with Van der Hoeve–de Kleyn's syndrome This appears, however to be only partly true Nager on numerous occasions has declared his agreement with the theory of a close connection between osteogenesis imperfecta and otosclerosis His personal contribution however to support this opinion seems to be limited to the finding of an otosclerotic bone focus in a temporal bone from a patient with blue sclerae—but without any osseous fragility

Shambaugh (in Coates, Schenk & Miller's *Otolaryngology*) states that he has performed a fenestration in 3 patients with this syndrome and that the findings during the operation were in no way different from the findings in otosclerosis generally

Clerc & Deunier also report the results of stapes mobilisations in three cases of Van der Hoeve–de Kleyn's syndrome. They have also observed changes indicating otosclerosis. However these observations are contradicted by Soov having operated on 4 cases in which he did not find any anchylosis of the stapes

At the Rikshospital in Oslo our interest in this syndrome of Van der Hoeve–de Kleyn was aroused during the autumn of 1960 when we were able to operate on 2 cases—and in both found anomalies of the stapes which did not seem to have been observed earlier

Going through our archives two more operated cases were found of which one almost certainly and the other possibly demonstrated the same anomalies. The identity of these changes however were not at that time acknowledged

The four cases were discussed in the Norwegian Oto-Laryngological Association in November 1960

In addition I have quite recently been able to operate the other ear of one of these patients—and found the same changes in the stapes The cases will be briefly discussed

Case I 41 year-old female Several of the nearest relatives had blue sclerae repeated fractures and impaired hearing The patient also showed blue sclerae and as a child had two fractures There had been buzzing in the ears and loss of hearing from the age of 20

There was mechanical (conductive) impairment of hearing symmetrical in both ears, which might well be consistent with otosclerosis

Stapedolysis was performed After loosening of the ear drum, the stapes appeared It was palpated with a probe and was not fixed but unusually mobile The mobility however was limited to the capitulum and the adjacent parts of the crura while the stapedial plate remained immobile

The cause of this was that the crura in the area adjacent to the plate were *degenerated* into thin threads of connective tissue, in part adherent to the facial nerve

These thin threads of connective tissue were *then removed* and likewise the rest of the crura with the capitulum The plate now appeared normal No otosclerotic changes were found either in the plate or in the adjacent *bone*

Fenestration performed at a later date did not give any hearing improvement The removed part of the stapes was found to be pathologic as the capitulum and the crura were unusually slender

In the area of the capitulum and the collum two cavities were found *lined with the epithelium of the normal middle ear*

Both crura were irregular At the end of one a small necrotic area was seen (Fig 1)

Case II 47 year-old male He had one child a daughter 15 years old, with blue sclerae, repeated fractures, but good hearing ability

The patient had blue sclerae and had repeated hospitalisations on account of fractures. Buzzing was present in the ears, and his hearing was gradually declining from the age of 36 On admission there was a substantial loss *of hearing of a mainly mechanical type* Stapedolysis was performed.

When the ear drum had been loosened, the stapes was clearly *visible* It was found to be unusually mobile and on close inspection both crura in the area of the plate were found to have degenerated into fibrous threads. The capitulum *and the adjacent parts of the crura were removed. The plate* had a normal appearance It was perforated at a single point and seemed to be of normal thickness. Neither the plate nor the adjacent area showed any structural changes which might suggest otosclerosis.

Fenestration at a later date did not result in any improvement of hearing ability

The removed parts of the stapes showed the same curious characteristics *as in Case I—Cavities lined with epithelium* within the area of the capitulum and collum—and deformed and structurally altered crura (Fig 2)

Case III 53-year-old-female.

A number of the nearest relatives were suffering *from the syndrome of* Van der Hoeve–de Kleyn The patient had blue sclerae and numerous fractures.

There had been buzzing in the ears and loss of hearing from the age of 46

On admission (Sept. 58) there was considerable loss of *hearing, mainly* of a conductive type as is common in otosclerosis.

Mobilisation of the stapes in the *left ear* was performed When the ear drum had been loosened the stapes was found to be quite mobile as far as the capitulum and *the adjacent* parts of the crura were concerned. The plate however did not accompany the movement In the records describing

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stapes and the crura were particularly mobile, which was presumably due to an unintentional fractura during the operative procedure.

The fenestration was completed in the usual way with a modest improvement of hearing ability as a result.

Case V The right ear of *Case III* On admission (March 1964) there was still a predominant hearing loss of the conductive type symmetrical in both ears. If the findings proved to be the same as in the other ear it was planned to implant a polyethylene strut between the incus and the plate.

When the ear drum had been loosened an unusually mobile stapes was again found

As in the previous case, the stapedial plate did not accompany the movement, on account of the crura being degenerated into fibrous threads.

The capitulum and crura were removed. The plate and the surrounding bone were of normal appearance

A polyethylene strut was placed between the plate and the lenticular process.

This installation proved easy but did not lead to any improvement of hearing, the reason being that the strut was obviously too short It was removed and replaced by a longer one, but during this process the plate loosened and became displaced half way into the labyrinth.

Obviously the plate had been very loose and since it was now out of function it was removed

A piece of fat was placed in the open fenestra ovalis and a polythylene strut (*ad modum* Shea) was placed with the pointed end on the fat and the other end around the process. The result was a considerable improvement of hearing ability which was also present when controlled six months later

The removed part of the stapes showed the same anomalies as previously mentioned—a delicate, slightly deformed crura and epithelium-lined cavities in the area of the capitulum and collum. In addition to these observations, one is reminded that both Sooy in four cases and Herberts *et al* in one case found what we call a mobile stapes. Their findings are not described more precisely but it would seem reasonable to assume that these might be the same anomalies as in our cases.

DISCUSSION

From an otological point of view the widespread interest in the syndrome of Van der Hoeve-de Kleyn is possibly due to the presumed connection between osteogenesis imperfecta and otosclerosis, which might throw some light upon the pathogenesis of otosclerosis.

Strictly speaking, only Ruttin's and Gimplinger's cases from 1922 and 1936 can represent any arguments for a connection.

In both report osseous changes were seen to be localized to a limited



FIG. 1 Stapes, cas 1 N te th two pithelium lined ca ities in the corpus.

FIG. 2. Stapes, case 2. Also here avities are seen in the corpus, and the crura are stru turally altered

the operation, the explanation was that the lack of acompanying movement of the plate obviously was due to some unusually slender flexible and delicate crura The plate appeared normal It was mobilized i e loosened from its surroundings, which was unusually easy

The results was a spontaneous improvement of hearing but with a relapse to pre-operative status in a short time

Case IV 44-year-old male The patient s father had blue sclerae and innumerable fractures, but had good hearing into advanced age

The patient had blue sclerae and repeated fractures

There had been loss of hearing from the age of 40 On admission there was a relatively considerable loss of hearing predominantly of the mechanical type almost symmetrical in both ears.

The case was considered to be otosclerosis. Fenestration of the right ear was performed

In the records from the operation it is emphasized that the head of the

factory results. These findings may be supported, while on the other hand considerable improvement of hearing was obtained by stapedectomy in one of our cases.

How these anomalies of the stapes have arisen can hardly be explained by our observations alone. Considering the nature of the anomalies and their uniformity from case to case, it seems reasonable to regard these as an expression of a generalized osseous disease—osteogenesis imperfecta.

This opinion is supported by the histological findings reported by Hall & Røhrt in the Norwegian Oto-Laryngeal Society, September 1962.

ZUSAMMENFASSUNG

Osteogenesis imperfecta, auch Van-der-Hoeve-de-Kleyn-Syndrom genannt, wird durch blaue Skleren, Fragilitas ossium und Schwerhörigkeit gekennzeichnet. Früher haben mehrere Autoren die begleitende Schwerhörigkeit als ein Resultat der Otosklerose und war identisch mit Otosklerose betrachtet. In den letzten Jahren dagegen gibt es Autoren, die eine solche Deutung der Schwerhörigkeit bezweifeln. Der Verfasser gibt einen Bericht von vier Fällen, die an Osteogenesis imperfecta leiden, von denen fünf Ohren mit Stapesmobilisierung operiert worden sind.

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area in the stapes and the sorrounding bone as is common in otosclerosis. However it seems obvious that these patients suffered from osteogenesis imperfecta *and* otosclerosis.

The interpretation of the histological picture seen in relation to the asserted conformity between the two diseases seems controversial. To quote Altmann

"Since bone tissue reacts in identical ways as a result of many different stimuli histological similarity or even complete likeness, does not necessarily tell us anything about the basic cause and thus nothing about a possible relationship

Likewise the presence of a conductive loss of hearing in the two diseases can in no way be interpreted as an expression of an intimate connection between the two

In our cases suffering from the syndrome of Van der Hoeve–de Kleyn part of the stapes crura were found to have degenerated into thin fibrous threads in four of their ears. In the fifth ear the same anomaly had possibly been present

Beyond doubt this anomaly can completely explain the conductive component in the patients impairment of hearing Thus the assumption of otosclerosis must be superfluous in these four possibly five ears, unless one would postulate that both a fibrous degeneration of the crura and an otosclerotic fixation of the plate existed, which seems unlikely

Moreover this is contradicted by the findings in Case no V where the plate was obviously very loosely placed in the fenestra ovalis.

These four or possibly five ears naturally do not allow any conclusions about the cause of the loss of hearing in the syndrome of Van der Hoeve–de Kleyn generally However it is justifiable to state that they represent serious reasons for doubting the validity of the present general opinion

If Soov's four cases and the single case of Herberts *et al* may be included—which seems justifiable—our reasons for doubt are still more strengthened This sum of ten ears seems to be a considerable number when seen in comparison to Ruttin and Gimplinger's two cases– and the fact that the syndrome of Van der Hoeve–de Kleyn must be considered a rarity

In addition to this there is reason to doubt a connection between osteogenesis imperfecta and otosclerosis on purely clinical grounds

Ruttin proposed that the loss of hearing in several of his patients was due to laesio cochlearis as he expressed it, i e a neurogenous type of hearing loss According to Clerc and Deumier the same observation was made by numerous authors later on—and we have also seen the sensori neural type of hearing loss in connection with blue sclerae and osseous fragility Sometimes we have found a quite considerable loss of hearing down to complete deafness—which is unusual in otosclerosis

In addition to this we must consider the fact that fenestration in the syndrome of Van der Hoeve–de Kleyn is reported to give rather unsatis

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THE STAPES IN OSTEOGENESIS IMPERFECTA

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Referring to cases of osteogenesis imperfecta presented by Ophelm in the present issue the authors describe the histological findings in the stapes of a newborn suffering from this disease. It is demonstrated that the actual stapes was abnormal, its crura being fragile and incomplete whereas the footplate and its surroundings were normal, in contrast to the observations in otosclerosis.

Ophelm (1967) has compared the findings in osteogenesis imperfecta (also called the syndrome of Van der Hoeve–de Kleyn) and otosclerosis. From his report it is seen that histologic investigations in these cases are scarce and that, in view of his findings, the old conception of the two diseases being identical concerning the cause of the loss of hearing must be revised.

This syndrome includes blue sclerae, fragilitas ossium and hardness of hearing. Of course this triad, on account of its multifarious clinical manifestations, has inspired many investigators, but despite the ample literature the aetiology of the disease still remains obscure. The commom assumption is that a dominant mutation must be present (Bauer 1920, Fuss, 1920, v. Seedorf 1949). The disease is classified according to its three different manifestations: osteogenesis imperfecta congenita, tarda gravis and tarda levis (v. Seedorf 1949). In the first congenital type the individuals usually die before their hearing can be evaluated. In the second and third types the patients become hard of hearing at about thirty years of age, which corresponds to the circumstances in otosclerosis. However, in osteogenesis imperfecta the loss of hearing becomes more pronounced and cochlear or neural defects are usually involved. Thus, there is a divergence between the two diseases concerning the loss of hearing, as there are concerning the other characteristics.

Blue sclerae are reported in connection with otosclerosis in 69 per cent (Fowler 1952) but in connection with osteogenesis imperfecta in 95 per cent. The fragile skeleton is a dominant phenomenon in osteogenesis imperfecta, but is seen very seldom in connection with otosclerosis.

Supporting the view expressed by Ophelm that the two diseases are also essentially different concerning the middle ear, a case is presented in which histological examination of the stapes was performed.

Our case was a newborn female with healthy parents and no cases of either osteogenesis imperfecta or otosclerosis in the family. The child was

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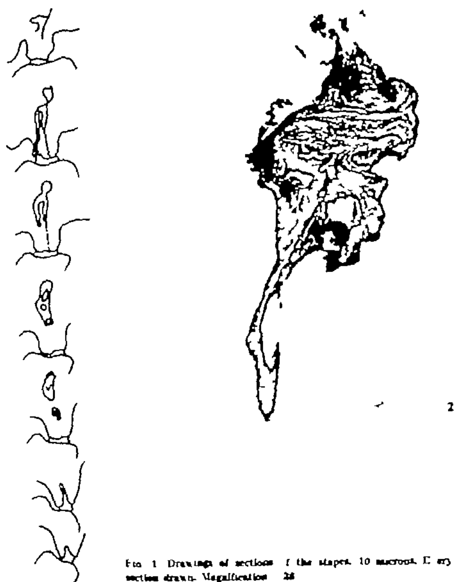


FIG. 1. Drawings of sections of the stapes, 10 microns. Every 10th section drawn. Magnification 28.

FIG. 2. The stapes, mid-line section.

An important objection, however, to the validity of our assumption lies in the fact that these were preparations from a newborn, and the question then arises: At what age does the earliest stages of otosclerosis occur?

In the literature it is seen that Manasse (1913) found otosclerosis in a 3-year-old, and Guild (1930) states that otosclerotic changes may begin as early as the end of the first year of postnatal life. Thus it is an open question whether otosclerotic foci might have developed in the case of a survival, and whether it is possible to detect earlier foci.

born two weeks premature weight 2960 g, length 44 cm The extremities were plump and X rays revealed multiple fractures in the arms, legs and costae The calvarium was soft and its sclerae blue. However the nourishment of this child met with no difficulties and its weight was gaining until it acquired a fever and died of pneumonia on the 25th day of life

At autopsy the lungs were found to be juvenile and stuffed, otherwise there were no pathological findings in the viscera including the parathyreoid glands.

The appearance of its bony structure is of special interest

The calvarium was soft, consisting mostly of connective and cartilaginous tissue Multiple fractures were shown in the extremities and in the costae around both of which was a rich formation of callus.

The temporal bones were preserved in formaline and later decalcinated and sectioned As a preparation of the cochlea was then out of question our interest concentrated on the middle ear especially the stapes and its surroundings

The stapedial joints showed no abnormalities, and especially no otosclerotic foci None of the localized patches of hyperplastic bony lamellae heaps of osteoblasts and the great number of capillaries usually seen in otosclerosis were present On the contrary the joints connecting the stapedial plate and the oval window were quite normal and no obliteration was found

Thus in this case, where the clinical and pathological findings confirmed the diagnosis osteogenesis imperfecta, any resemblance to otosclerosis can be ruled out

The fact that the footplate and its surroundings were found normal brought forth the next question What about the structure of the stapes itself? And this brings us to the main point of our investigation The pathological findings in the stapedial structure might if found in grown ups, explain a loss of hearing of the mechanical type

The stapes was decalcified and the following paraffin cast sectioned and stained Fig 1 shows a drawing of every 10th section and Fig 2 is a photograph of the stapes

In the first place it seems obvious that this is not a normal stapes The corpus is deformed, the crura frayed thin in some places thread like and the edges as seen in the photograph are irregular In none of the sections were the crura found solid all the way it is seen that one crus ends as a pointed tip towards another at the footplate with only a fibrous connection and the other is only seen as a thin fragile thread These findings correspond with those referred to by Opheim in his cases of osteogenesis imperfecta In conclusion it may be stated that this stapes would have prevented the perception of sound due to its mechanical properties. The pathological findings, however were not of otosclerotic nature as the footplate and its surroundings were quite normal whereas the stapedial crurae were abnormal fragile flexible frayed and incomplete

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BÉKÉSY TRACINGS IN NORMAL LISTENERS FOLLOWING CONTRALATERAL MASKING

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Békésy fixed-frequency tracings for continuous tones were studied in normal listeners before and after masking the contralateral ear with wide-band noise of low and moderate intensity. In many cases, the effect of contralateral masking persists beyond the masking period, and in some cases the effect is even more pronounced after the exposure to noise than during the exposure, excessive threshold drifts being observed. A weak masking of one ear is quite regularly followed by tinnitus in the opposite ear and in this ear exclusively.

In our investigations of contralateral masking and Békésy audiometry by the method of Jerger in normal listeners, we found that masking of the non-test ear during the threshold recording resulted in the following changes. (1) Reduction in tracing amplitude in the fixed-frequency curves at 1000 and 4000 cps. This amplitude reduction was most pronounced in the continuous tone tracings (the C tracings) but the change was also well marked in the tracings recorded with interrupted tones (the I tracings). (2) Separation between I and C fixed frequency tracings at the frequencies mentioned. The separation was due to the reduction in the tracing amplitude of the curve as well as to the fact that the threshold changes resulting from masking were greater for C than for I. The above changes can presumably be ascribed to the influence of masking on the adaptation characteristics of the test ear. In the investigations, the fixed frequency curves were recorded with masking for a period of 3 minutes. The effect of contralateral masking was observed to develop quite gradually: the tracing amplitude at 1000 cps, for example, was found to be noticeably smaller during the 3rd minute than during the 2nd minute. During the experiments, it was observed that the changes in the curves could persist after the noise was switched off.

The present investigation was made to evaluate the after-effect of contralateral masking. As in the previous investigations, the duration of each masking period was 3 minutes. Two situations were selected for investigation. In the first, the non-test ear was exposed to noise and the test tone

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Nevertheless, we found it of interest to observe that the appearance of the stapes in a newborn suffering from osteogenesis imperfecta was consistent with and an explanation of a loss of hearing

ZUSAMMENFASSUNG

Auf vier Fälle von Osteogenesis imperfecta hinweisend (siehe Opheims Artikel dieses Heftes) beschreiben die Autoren den histologischen Befund des Steigbügels bei einem Neugeborenen mit Osteogenesis imperfecta. Dieser Steigbügel ist abnorm mit fragilen und unvollständigen Schenkeln Die Fussplatte und ihre Umgebung dagegen sind normal im Gegensatz zu den Befunden bei Otosklerose

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masking, the post masking tracing behaviour of the subject was always compared with the pre-masking behaviour in the session in question. The results were analysed both with regard to thresholds and to the mean number of pen swings per minute. The threshold values were determined for the last 10 seconds of each period of 1 minute, as the midline between tops and bottoms of the tracing excursions. The number of pen swings per minute gives the number of separate pen strokes (pen reversals) and is taken as a measure of the mean tracing amplitude, as the two values are inversely proportional.

RESULTS

The effect of a preceding contralateral masking varied individually and even in the individual subject the effect was not constant. Thus, in experiment I the shifts in the same individual were not always in the same direction after masking levels of 70 and 90 dB and in experiment II, where the investigation with 90 dB masking was performed twice, the post masking tracing behaviour was not always the same in the two sessions.

1 *Thresholds*

Table 1 gives the results for experiment I. The threshold for continuous tone is indicated in relation to the subject's initial threshold for *I*. A statistical analysis by means of the *t*-test showed that the mean difference between pre and post masking threshold levels did not differ significantly from 0. In one of the subjects, however, marked shifts were found. In

TABLE 1 *Continuous tone thresholds in experiment I before and after contralateral masking*

The values indicate differences (dB) between C thresholds and initial threshold for *I*. Positive values indicate that the threshold for C was found at a higher sound pressure. The pre-masking determinations from the 1st and 2nd session are combined in the table.

Test tone frequency		Before masking		After 70 dB masking		After 90 dB masking	
		End of 1st min	End of 2nd min	End of 1st min	End of 2nd min	End of 1st min	End of 2nd min
250 cps	Mean	0.7	1.0	1.8	0.5	2.3	2.9
	Median	0.3	1.0	0	0	0.8	1.8
	Range	5.0 to 8.5	11.0 to 10.0	3.0 to 15.0	−7.0 to 10.0	5.0 to 1.0	−2.0 to 13.0
1000 cps	Mean	2.1	2.8	2.9	5.2	2.2	3.2
	Median	1.3	2.3	3.0	3.5	0	0.3
	Range	3.0 to 7.0	1.5 to 12.0	1.0 to 12.5	0 to 16.5	−7.8 to 21.8	7.5 to 20.0
4000 cps	Mean	4.5	6.0	4.3	8.6	5.5	8.5
	Median	4.0	3.8	2.0	4.0	3.5	2.0
	Range	2.0 to 18.0	0.5 to 19.5	4.0 to 21.5	7.0 to 40.0	3.0 to 21.0	1.5 to 20.0

was not introduced until immediately after the noise was switched off In the second situation the subject was asked to trace his threshold during the exposure to the contralateral masking, and to continue tracing after the masking was switched off Supplementary to the above, we examined whether in a 3 hour session in which the contralateral ear had been exposed repeatedly to masking fixed frequency curves recorded towards the end of the session differed from curves recorded at the commencement of the session The curves for continuous tone were of particular interest, as the changes are most pronounced in these

PROCEDURE

The investigation comprised 10 normal listeners aged 18–23 years Seven of them had taken part in the previous investigation of Békésy audiometry and contralateral masking, while the other 3 were given a practice session before the actual experiment. The apparatus used was as described previously the calibration is now according to the ISO 1964 Standard The test tone was delivered by ordinary headphone, the noise (wide-band white noise) by insert type receiver The rate of attenuation was 125 dB/min Each subject was examined in 2 sessions at an interval of about 3 weeks. All investigations were made at 4000 1000 and 250 cps always in the order indicated In spite of the risk of a time-order-effect, we chose to keep the sequence fixed in order to reduce the number of variables The following investigations were made

At the commencement of each session threshold tracings were made with interrupted and continuous tones for 2 minutes each Then followed

Experiment I

This experiment consisted of threshold measurements for 2 minutes with continuous tone after masking had been delivered to the contralateral ear for 3 minutes In the first session 70 dB SPL was used, in the second session 90 dB

Experiment II

Here the subject traced his threshold during the masking period of 3 minutes After the noise was switched off the subject continued to trace for 2 minutes The experiments were performed at both 70 and 90 dB SPL during the first s ssion During the second session only a masking level of 90 dB was used

Finally at the end of the session the threshold measurements for *I* and *C* were repeated for 2 minutes each

All tracings were commenced from the level of inaudibility and the subject was allowed 15 seconds to find the threshold These 15 seconds were not included in the calculations. In evaluating the influence of

TABLE 2. *Continuous tone thresholds in experiment II in which the subject traced his threshold while contralateral masking was applied*

The values again indicate the differences (dB) between the threshold level measured and the subject's initial threshold for *I* being positive when the threshold for C was the poorer. The 90 dB condition was investigated twice, and these measurements are combined in the table

Test tone frequency		70 dB contralateral masking			90 dB contralateral masking		
		End of masking	End of 1st min	End of 2nd min	End of masking	End of 1st min	End of 2nd min
250 cps	Mean	2.0	1.8	0.8	3.2	2.5	1.7
	Median	0.5	0.3	1.0	2.0	−0.5	1.0
	Range	−4.0 to 15.0	−6.0 to 15.0	−5.0 to 8.5	−7.0 to 42.5	−6.5 to 35.5	−7.0 to 40.5
1000 cps	Mean	6.4	7.0	6.4	10.3	7.4	6.8
	Median	3.3	4.3	4.0	9.1	4.3	3.4
	Range	1.0 to 13.6	2.0 to 22.0	3.0 to 26.3	−0.5 to 46.5	−3.5 to 38.5	−9.0 to 41.5
4000 cps	Mean	12.0	12.3	12.4	12.1	9.6	14.3
	Median	8.8	4.0	6.3	11.9	9.5	5.9
	Range	1.0 to 38.0	2.0 to 53.0	0.5 to 47.5	>−30.0 to 45.0	1.0 to 51.0	−2.5 to 63.0

threshold was −10 dB at the termination of masking period after masking the threshold improved further so that after the lapse of 2 minutes it was 25 dB better than the initial value for *I* and 23 dB better than average normal threshold

A comparison of the tracings at the commencement and termination of the session gave the following results At 1000 cps and 4000 cps, the *separation between midpoints of the I and C tracings* was on the average slightly less at the end of the session than at the *commencement* (at 1000 cps, the mean decrease was 1.2 dB, at 4000 cps it was 1.5 dB) at 250 cps the separation increased by 3.9 dB on an average

2 Number of pen swings per minute

Experiment I Figs. 5 *a b* and *c* show the *number of pen swings per minute* after masking, in relation to the number before masking. The values

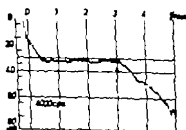


FIG. 4 C-tracing from subject S. H. The contralateral ear was masked with 90 dB during the first part of the tracing. The masking was switched off at *t*

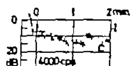


Fig 1

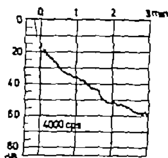


Fig 2

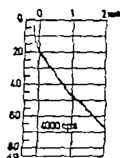


Fig 3

Fig. 1 Pre-m king tracings for int rmittent (I) and ontinuous t n (C) from subject S. H.

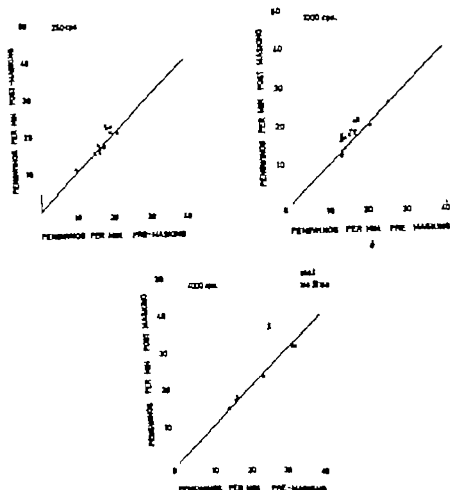
Fig 2. C-t acing from the same subject recorded afte exposure of the n n-test ear to 0 dB wide-band noise fo 3 minutes. The tracing in thi case wa followed longer than the usual two minutes, in iew of its remarkable course

Fig. 3 C-tracing recorded after contral teral m sking of 50 dB int nsity f r 3 minutes. The curve was recorded during a third, suppl me tary sessi n

Figs 1 and 2 the thresholds before and after 70 dB masking are shown. After exposure to 90 dB the change was less pronounced This subject, S H., was examined in an extra session in which 50 dB masking was used the effect was striking (Fig 3) These pronounced threshold drifts, which continued as long as the threshold was followed were only found at 4000 cps. Subject S H is a 20-year-old medical student, in perfect health and with a completely negative anamnesis

Table 2 shows the results for experiment II The table gives the thresh old value at the end of the masking period, and also 1 and 2 minutes after the cessation of the noise As previously the threshold values are indicated in relation to the subject s initial threshold for *I* In the table, the results of the two experiments in which 90 dB masking was employed are com bined As will appear from the median values, shifts at 250 cps were usually small At 1000 and 4000 cps, the threshold generally improved only gradu ally after masking was switched off and without reaching the pre masking levels of Table 1 completely In two of the subjects, switching off the noise resulted regularly in a definite worsening of the threshold (7.5 to 38 dB) so that at times the curve did not stabilize in the course of the follow up period Fig 4 shows the result for subject S H

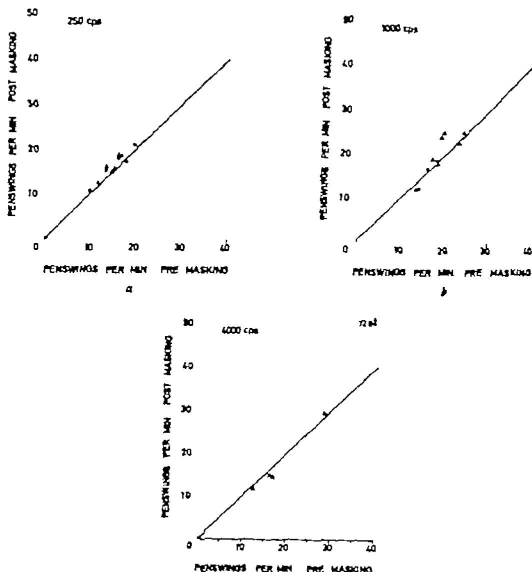
A somewhat unexpected result was that at 4000 cps, the C threshold in one of the subjects gradually became more and more acute during contra-lateral masking of 90 dB Thus, after 3 minutes the threshold was 25 dB better than the pre-masking threshold for *I* On repeating the experiment the threshold became >30 dB better than the threshold for *I* (the attenua tion of the audiometer being insufficient for the recording) On switching off the noise, the threshold was normalized on both occasions to within ±3 dB. This subject was also examined in a 3rd session and here the



Figs. 5 a, b and c. The mean number of pen swings per minute measured over a period of 3 minutes after contralateral masking, in relation to the corresponding number before masking. Results from experiment II. Masking condition: ● 60 dB SPL, △ 90 dB SPL (1st session), 90 dB SPL (2nd session).

respectively. At 1000 cps, the mean increase was 2.7 ±1.2 and 2.9 ±0.9, respectively, while at 4000 cps the mean increase was 8.2±4.6 and 5.6±3.8 pen swings per minute. As indicated by the asterisks, the mean values of the changes at 1000 cps were found to differ significantly from O at the 5 level. At 4000 cps the differences were not statistically significant.

Comparing the values at the start and at the termination of a session, no systematic variation was found. At 1000 cps and 4000 cps, the difference was very slight (an average of 0±0.5 and −0.4±1.4, respectively). At 250 cps, the difference was slightly greater −1.4±1.6 excursions per minute.



Figs. 5 *a* *b* and *c* Th mean n mbe f pen swings pe minute measured o e a period of 2 minutes aft r contralateral masking, in relation to th corresponding numbe be- f re maski g. Results from e periment I Masking co dition ● 70 dB SPL △ 90 dB SPL.

are mean values for the complete 2 minute period When the values for the 1st and 2nd minutes were plotted separately the same overall picture was obtained According to the *t* test the mean change did not differ significantly from 0 either after noise at a level of 70 dB or 90 dB Combining the data from both masking conditions the change at 1000 cps was 1 3 ± 0 9 and at 4000 cps, 1 8 ± 2 5 pen swings per minute

In a corresponding manner Figs. 6 *a* *b* and *c* show the result from ex periment II At all 3 frequencies, there is a preponderance of observations above the 45 line i e the number of pen swings is increased after masking At 250 cps, however the mean increase in the number of excursions per minute amounted to only 0 6 ± 1 8 and 1 4 ± 1.3 after 70 and 90 dB masking,

body or to the auditory cortex. The threshold drifts observed in the present investigation are too great to be compatible with such a concept. Alterations must also occur at lower levels of the auditory pathways, presumably even in the cochlea. These alterations could be mediated through efferent fibres.

To sum up the present investigation, it may be said that masking of one ear is often followed by changes in the threshold function of the contralateral ear which persist for minutes. These changes are not a simple function of the exposure to noise, as in general they are only pronounced when the subject has traced his threshold during the masking period. In some cases, the changes are considerably greater after masking than during masking.

ZUSAMMENFASSUNG

Man hat bei Normalhörenden die frequenzkonstanten Békésy Kurven für stetige Töne vor und nach der Maskierung des kontralateral n Ohres mit weissem Geräusch von niedriger und moderater Intensität untersucht. In vielen Fällen dauert der Effekt der kontralateralen Maskierung bis über den Zeitraum der Maskierung an, und in einigen Fällen ist die Wirkung sogar noch ausgesprochener — nachdem die Stimulation des kontralateralen Ohres zu Ende ist — als während derselben mit excessiven Schwellenänderungen zur Folge. Eine ganz schwache Maskierung des einen Ohres wird regelmässig von Säuseln im gegenüberliegenden Ohr und zwar in diesem Ohr allein, gefolgt.

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DISCUSSION

In experiment I one of the subjects showed pronounced temporary changes in threshold after low level contralateral masking The threshold drifts were of the same order of magnitude as those seen in patients with acoustic neuromas, but were observed only at 4000 cps They were accompanied by a considerable reduction in tracing amplitude The other subjects showed no definite effect During this experiment two of the subjects noted tinnitus in the test ear on termination of the masking In Theilgaard's investigations (1951) of auditory fatigue some of the subjects experienced a bilateral buzzing after unilateral stimulation This never occurred unless the intensity of the stimulus (always a pure tone) was higher than 85 dB and a buzzing exclusively in the non stimulated ear occurred in only 7 out of 214 experiments. In order to evaluate the phenomenon we exposed 10 normal listeners to 50 dB unilateral masking for 3 minutes after which the headphones were disconnected 9 reported that after masking there was a faint seething or ringing sound in the non stimulated ear The sound gradually decreased but generally persisted for 30 to 45 seconds None of the subjects experienced tinnitus in the masked ear If 90 dB was applied the sensations were more variable.

In experiment II it was noteworthy that at 1000 cps and 4000 cps, two of the subjects had the most pronounced threshold changes after the masking was switched off After masking at a level of 90 dB the threshold decayed in both subjects to 60–70 dB hearing level in the course of 2 minutes. For the rest of the group it was characteristic that the changes in threshold resulting from masking disappeared only gradually In a previous study we showed that at 1000 cps and 4000 cps, the tracing amplitude is reduced by simultaneous masking of the contralateral ear In the present investigation we found that measured over a period of 2 minutes the mean tracing amplitude at 1000 cps was smaller after masking than before There is thus a pronounced tendency for the reduction to persist after the noise is switched off

Among the after-effects to contralateral stimulation described by previous authors, the so called hetero-lateral dip" ought to be mentioned Following exposure of one ear to a pure tone of fatiguing intensity a dip may sometimes be demonstrated also in the non-exposed ear This was described by Rawdon Smith (1935/1936) confirmed by Greisen (1951) and by Theilgaard (1951) and more extensively studied by van Gool (1952) According to the last named author the heterolateral dip is always considerably smaller than the dip in the directly stimulated ear It does not exceed 25 dB, and it cannot be produced in persons with complete one-sided deafness In the Greisen and van Gool studies an inverse reaction was noted in a few exceptional cases after the stimulation there was a definite improvement of the threshold of the heterolateral ear Van Gool ascribes the heterolateral dip to processes localized to the medial geniculate

MATERIALS AND METHODS

Maxillary mucosa, mucosa of the inferior turbinate and nasal polypi were obtained by operation from patients with sinusitis. Examined specimens consisted of 11 cases of maxillary sinus mucosa, 10 cases of nasal polyps and 7 cases of mucosa of the inferior turbinate. These mucosa were added to one half of wet tissue weight of 0.2% cetyltrymethylammonium bromide solution. The mixture was homogenized and then centrifuged at 10,000 r.p.m. for ten minutes at 0 C. The supernatant was used for the experiment.

Electrophoresis and immunoelectrophoresis were performed using a 26 mm × 76 mm microscopic slide. A 1.5% agar solution prepared in veronal buffer pH 8.6, ionic strength 0.05 was used as a medium for electrophoretic separation. Two parallel round wells of 2 mm diameter were cut in the agar plate. For electrophoresis to analyze the fibrinolytic enzyme, these two wells were filled with the same sample. Electrophoretic separation was carried out for a period of 120 min at 6 mA per one plate coupled with veronal buffer at pH 8.6 with an ionic strength of 0.05 at 0 C. On completion of electrophoretic separation, a longitudinal cut was made in the midline of the agar plate, and one side of the cut agar was sectioned in 3 mm of its width. Then each section of agar was placed on the fibrin plate prepared by the method described below. Following this, fibrin plates were incubated for 18 hours at 37 C. After incubation the lyzed zones were measured respectively. The other side of the cut agar was placed in a dry heat oven and after drying was stained with amido black dye for one hour. To remove excess dye it was washed with a solution of 5% glacial acetic acid.

For immunoelectrophoresis, the upper well was filled with the human serum and the lower well with the extract of nasal mucosa. After electrophoretic separation, a longitudinal trough 2 mm in width was cut out and filled with horse anti-whole human serum. The plate was placed in Petri dishes containing moistened filter paper and was incubated at 37 C for 24 hours to permit diffusion and reaction of the antigen–antibody system. This was washed for three days in phosphate buffered saline, pH 7.6, with changes twice daily of buffered solution. After this washing, the agar plate was washed two or three times an hour with distilled water and then heat fixed and stained by amido black dye. Bovine fibrinogen of Armor Laboratories was dissolved in a veronal buffer pH 7.4, making 0.2% solution. Varidase streptokinase preparation of Lederle Laboratory and bovine thrombin topical of Mochida Pharmaceutical's was used. Nine ml of 0.2% fibrinogen solution was mixed with 0.3 ml of 100 units per ml thrombin in a Petri dish and a fibrin plate was made. In order to detect a streptokinase (SK)-activated enzyme that is plasmin, 100 units of SK were added to a Petri dish before forming the fibrin plate. Horse anti whole human serum *

* kindly offered by the Department of Pharmacology of Nihon University School of Medicine Tokyo (Prof. M. Kobayashi)

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THE ELECTROPHORETIC ANALYSIS OF THE "NASAL FIBRINOLYTIC ENZYME"

Y SASAKI

From the Department of Otorhinolaryngology Nihon University School of Medicine Tokyo Japan

Nasal mucosa has a specific proteolytic enzyme which the author calls the "nasal fibrinolytic enzyme" In the work described in this paper the relationship between the nasal fibrinolytic enzyme and the SK activated enzyme in nasal mucosa and human blood serum was investigated by electrophoresis and immunoelectrophoresis The nasal fibrinolytic enzyme was located in the neighbourhood of the β-globulin fraction. The SK activated enzyme in nasal mucosa was strongest in the β globulin fraction and in this respect is similar to human blood serum The distribution pattern of the SK-activated enzyme in the nasal polyp was more closely related to the blood serum than other nasal mucosa. By immunoelectrophoresis it was found that the nasal polyp seemed to have more properties similar to blood serum than other nasal mucosa The pathological and biochemical significance of the nasal polyp is discussed in the light of these observations

Chronic sinusitis has a variety of features in clinical and pathological types, amongst which the nasal polyp is one of the characteristic products. It is very important to investigate not only the morphology of sinusitis but also the tissue metabolism in the sinus mucosa in order to reveal the mechanism which maintains the chronicity of the inflammation

Sasaki *et al* (1959) have reported that nasal mucosa contains a proteolytic enzyme which has the action of fibrinolysis but not fibrinogenolysis, while tissues of the palate, pharyngeal tonsil etc., lack such a proteolytic enzyme Blood has a proteolytic enzyme called plasmin, which acts on fibrin and fibrinogen by activation of the plasminogen of zymogen From where does this proteolytic enzyme in nasal mucosa originate? Is there any relationship between this enzyme in the nasal mucosa and plasmin in blood? It will be necessary to clarify the character of the enzyme in nasal mucosa, which I termed the "nasal fibrinolytic enzyme" and then compare this with the proteolytic enzyme of other tissues. This paper deals with some observations of electrophoretic and immunoelectrophoretic studies carried out on an extract of nasal mucosa and blood serum



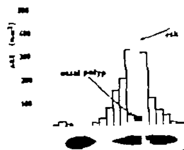


Fig. 3. Fig. 4.

Fig. 3. Electrophoresis of the extract of the maxillary mucosa and its fibrinolytic pattern.

Fig. 4. Electrophoresis of the extract of the nasal polyp and its fibrinolytic pattern.

certain enzyme which induces fibrinolysis after reaction with SK. The SK activated enzyme seemed to have a similar pattern in fibrinolysis to plasmin, which was demonstrated after the electrophoretic separation of human blood serum.

The author tried to discover whether nasal mucosa had the same protein as blood serum, using the method of immunoelectrophoresis.

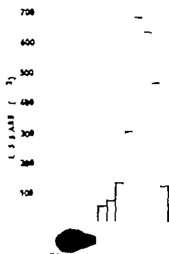
The protein in nasal mucosa reacting with horse anti-whole human serum would be the same protein as human serum.

The precipitation lines forming after the reaction of the extract of nasal mucosa with antiserum are shown in Figs. 5, 6 and 7. These extracts had several precipitation lines reacting with antiserum.

Generally speaking, the nasal polyp seemed to have more precipitation lines and more types of protein than other nasal mucosa. This observation



Fig. 5. Immunoelectrophoretic pattern of human blood serum (upper) and the extract of the maxillary mucosa (lower) obtained with horse anti-human serum. Amido black staining. The protein content was by the method of the Hitachi Hand Protein Refractometer: blood serum, 7.9 g/dl; the extract of the maxillary mucosa, 4.1 g/dl.



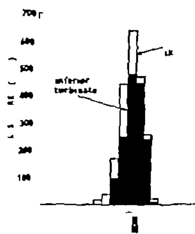


FIG 1 FIG 2.

FIG. 1 Electrophoresis of human blood serum and its fibrinolytic pattern after reaction with SK.

FIG. 2. Electrophoresis of the extract of th infe ior turbinate and its fibrinolytic pattern.

RESULTS

After electrophoresis of the human blood serum some sections of the agar plate brought about fibrinolysis in a fibrin plate containing SK It was found that the proteolytic enzyme existed between the α_2 globulin and a part of the γ-globulin The strongest activity was in the β globulin (Fig. 1)

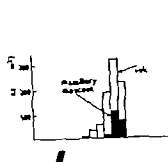
The extract of the mucosa of the inferior turbinate brought about fibrinolysis in the β globulin and extended to a part of the γ-globulin. The SK-activated enzyme in this mucosa of the inferior turbinate was in the neighbouring region of the α_2-globulin and extended to a part of the γ globulin and was a little broader than that of the mucosa of the inferior turbinate containing no SK (Fig 2)

The extract of the maxillary sinus mucosa brought about fibrinolysis in the β globulin, and extended to a part of the γ globulin The SK activated enzyme in the maxillary mucosa was in the α_2 globulin and extended to a part of the γ globulin This activity was a little broader than that of the maxillary mucosa containing no SK (Fig 3)

The nasal polyp was slightly active in the proteolysis in the β globulin and extended to a part of the γ-globulin but the SK activated enzyme was remarkably broader than that containing no SK and in some cases fibrinolysis appeared in the fraction of prealbumin (Fig 4)

The proteolytic enzyme against fibrin in the mucosa of the inferior turbinate maxillary mucosa and nasal polyps was most active in the fraction of the β-globulin region but not always parallel to the concentration of the β globulin

Each nasal mucosa contains a type of fibrinolytic enzyme and also a



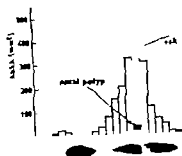


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Fig. 6 Immunoelectrophoretic pattern of human serum (upper) and the extract of the inferior turbinate (lower) obtained with horse anti-human serum. Amido black staining. The protein content wa by the method of the Hitachi Hand Protein Refractometer: blood serum, 7.0 g/dl the extract of the inferior turbinate, 4 6 g/dl.



Fig. 7 Immunoelectrophoreti pattern f human serum (uppe) nd the xtract of the nasal polyp (lower) btain d with horse anti human serum Amido black staini g. The protein cont nt wa by the method of th Hit hi H nd Protein R fractom ter blood serum, 7 9 g/dl the extract of the nasal polyp, 2.4 g/dl

supports the previous statement that there was a broader spectrum of the SK activated enzyme in the nasal polyp compared with other nasal tissues, even though the "nasal fibrinolytic enzyme occurs to a lesser extent in the nasal polyp than in other nasal structures.

DISCUSSION

The fibrinolytic enzyme in nasal mucosa appeared in the neighbouring region of the β globulin fraction after electrophoretic separation of the extract of nasal mucosa. This activity was not always proportional to the protein concentration of the β-globulin fraction and did not seem to be the same protein as the β-globulin This enzyme always stayed near the original well and proved to have little electrophoretic mobility

Many excellent investigations about plasmin, that is proteolytic enzyme in blood, have been reported during recent years. I reported a specific

fibrinolytic enzyme in nasal mucosa and in this report I comment on the character of this enzyme and plasmin by electrophoretic separation. I tried to elucidate the relationship of the nasal fibrinolytic enzyme and the SK activated enzyme in nasal mucosa.

Miura (1965) indicated that a proactivator of plasmin is present in nasal mucosa. But nasal mucosa might take up the serum protein into its tissue through the modification of permeability in blood vessels in the inflammatory process. The severer the inflammation, for example edema or nasal polypi, the more the permeability of blood serum increases.

Immunoelectrophoretic separation showed that the extract of the nasal mucosa had several protein fractions similar to that of blood serum and this similarity was remarkable in the nasal polyps. It is worth noting that ample protein was found similar to serum in the nasal polyp which is obtained by the least contamination of blood on operation.

In the nasal polyp the SK-activated enzyme was in the fraction of the -globulin and extended to the greater part of the γ-globulin, which is very similar to this enzyme's behaviour in blood serum.

In another report the author (1967) reported the presence of antitryptic action in the nasal polyp and its absence in the mucosa of the maxillary sinus and the inferior turbinate. This antitryptic activity was unstable against acid. Blood serum has a very high potency inhibiting trypsin activity and the majority of these antitryptic factors were destroyed by acid.

Plasminogen in blood serum converts into plasmin by activation of plasminogen by bacteriokinase and cytokinase. Plasmin forms a peptide such as bradykinins by breaking down protein and shows the pathological phenomen.

These experiments indicated that some metabolic pathways in the nasal polyp are similar to blood serum. From the analytical studies of the protein constituents of these tissues, comparative study of the SK activated enzyme in the nasal polyp and plasmin in blood serum, it was concluded that nasal polypi are under the influence of plasmin activity and other fractions in blood. Nasal mucosa had not only the nasal fibrinolytic enzyme but also the SK-activated enzyme and this SK activated enzyme in nasal polypi appeared in the fraction of prealbumin and the greater part of the γ-globulin region. This might be a characteristic of nasal polypi in chronic sinusitis.

ZUSAMMENFASSUNG

In der Nasenschleimhaut liefert ein spezifisches proteolytisches Enzym, das vom Verf. „nasales fibrinolytisches Enzym" genannt wird. Der Zusammenhang zwischen dem nasalen fibrinolytischen Enzym und einem von der Streptokinase aktivierten Enzym in der Naseschleimhaut oder in dem Menschenserum wird elektrophoretisch und immunoelektrophoretisch untersucht. Das nasale fibrinolytische Enzym befindet sich in der Nähe von β-Globulinfraktion. Das SK

aktivierte Enzym in der Nasenschleimhaut ist ebenso wie im Menschenserum im β-Globulin am stärksten Das Verbreitungsbild des SK aktivierten Enzyms im Nasenpolyp zeigt eine auffallendere Analogie zum Menschenserum als andere Nasenschleimhautteile Es wird immunoelektrophoretisch bewiesen, daß das Serumeiweiß im Nasenpolyp mehr als im Gewebe vom anderen Nasenschleimhaut teil eingenommen wird.

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HEREDITARY PROGRESSIVE PERCEPTIVE DEAFNESS IN A FAMILY OF 72 PATIENTS

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Of a family comprising 72 members, 12 females and 13 males were found to suffer from a hereditary progressive perceptive deafness. The inheritance is autosomal dominant, with complete penetrance. The development of the hearing loss follows a certain pattern. It involves the highest frequencies first, and at a later stage an additional low tone loss develops. Recruitment, demonstrated by the Metz recruitment test, was present in all the patients tested. Perstimulatory adaptation test (tone decay test) showed normal values in frequencies with a hearing loss less than 50 dB, but in several frequencies with a more pronounced hearing loss, there was a pathological threshold shift. The audiological results point towards a degenerative lesion in the cochlea, with a possible additional degenerative lesion in the more central structures when the hearing loss becomes more pronounced.

Both dominant and recessive inheritance have long been recognized as causes of perceptive hearing loss and deafness. It is now generally accepted that dominant inheritance leads to a progressive hearing loss, in contrast to the recessive trait which leads to an essentially stationary hearing defect (Albrecht, 1923 Popow 1934 Johnsen 1952 Dolowitz & Stephens, 1961 Huizing et al 1966) Exceptions to this rule have been documented by Johnsen (1954) and by Cawthorne & Hinchcliffe (1957) who have described cases with a progressive hearing loss apparently inherited in a recessive way

Reports on audiological studies of patients with a dominant hereditary progressive deafness are few and the results are to some extent controversial. Huizing *et al* (1966) found the hearing loss to be symmetrical purely perceptive affecting high frequencies first and most seriously. Plotting the mean hearing loss of the individual patient against age, they concluded that the hearing impairment proceeded most rapidly in the first three decades of life whereafter the progression slowed down. Using a special masking method and SISI test, they found recruitment in all their patients so tested. Perstimulatory adaptation test, carried out in a frequency where the hearing loss was moderate, showed results within normal limits. In patients with a similar hearing loss Dolowitz & Stephens (1961) did not find evidence of recruitment using monaural and binaural balance test. Perstimulatory adaptation test was, with a few exceptions, normal.

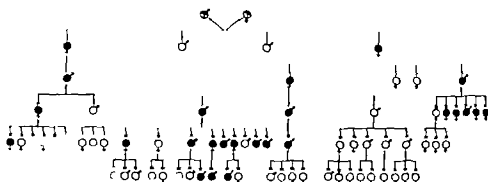


FIG. 1 Pedigree of the family examined. The inheritance is autosomal dominant with complete penetrance. ○ normal hearing, ● deaf ○ below 6 years of ag ⊥ audiometrically tested.

The present investigation of hereditary progressive perceptive deafness classifies the type of inheritance in the family examined it describes the development pattern of the hearing loss based upon repeated registrations in the individual patient and it reports the results of recruitment tests and perstimulatory adaptation tests

Inheritance

The present study is of a family comprising 72 members (Fig 1) with 25 members (12 females and 13 males) suffering from a progressive perceptive deafness The original couple lived in Verdal, North Trøndelag There is no information about their hearing Two sons had normal hearing and there are no known cases of deafness among their descendants. Two daughters developed a gradual hearing loss giving difficulties in social communications at 25–30 years of age Members of their families are well known in the area for their tendency to develop a gradual deafness from about 20 years of age

Fifty five of the family members could still be reached in this area and all of them volunteered to a routine ENT examination and pure tone audiometry A varying degree of perceptive hearing loss was found in 18 persons. All of them claimed to have had normal hearing during childhood and the first few years in elementary school Following the criteria of Glorig & Nixon (1962) 35 of the examined persons were found to have a normal hearing Two persons classified in Fig 1 as having "normal hearing had a sensori neural hearing loss. One who had served in the Army as artillerist had a typical noise induced hearing loss in his right ear with a dip to 50 dB and 65 dB for the frequencies 4000 Hz and 6000 Hz respectively The other person had a history of severe meningitis at 30 years of age followed by bilateral hearing loss, most pronounced in the lower frequencies Seven teen persons were either deceased or had moved far away from places

where hearing tests could be done. Based on anamnestical data deafness was diagnosed in 7 of them. As seen from the family tree the inheritance is of an autosomal dominant type, with complete penetrance.

Audiological Results

Many of the patients with a hearing loss had been examined in Namdal hospital previously. For 11 persons we had audiograms registered with intervals for a period varying between 3 and 15 years. It was thus possible to follow the steady hearing deterioration in the individual patient. In all 11 patients a progression of 30 dB or more in one or more frequencies took place during the observation period.

The progression of the hearing loss follows a definite pattern. Audiograms (Fig. 2) registered with intervals in 3 patients during different age periods exemplify the general impression.

Starting in the highest frequencies before 7 years of age, a hearing loss of about 60–80 dB gradually develops in frequencies above 1000 Hz. Although the low tone loss may start earlier, it now proceeds to 40–60 dB for frequencies below 1000 Hz. Further development leads to complete deafness for frequencies above 1000–2000 Hz, with greatly impaired hearing acuity for the lower tones. The condition may end up with total deafness which was diagnosed in 2 of our patients. The intervals between each hearing registration have been too irregular in most of our patients to allow any conclusion as to the possibility of the existence of different stages of "relative arrestation" (Huizing *et al.*, 1966).

Twelve patients with a varying degree of hearing loss were willing to travel the long distance to the hospital for a more extensive audiological examination. Recruitment was tested, using a Madsen Impedance Meter type ZO 61. In 4 patients the eventual presence of recruitment could not be expected to be demonstrated by this method. Their hearing loss was severe with total deafness for tones over 1000–1500 Hz, and in the lower frequencies the stimulus tone could be increased very little above the hearing threshold because of the output limit of the audiometer. All 8 patients tested had recruitment. In all of them the stapedius reflex, which normally is elicited by pure tone stimuli 0–90 dB above the hearing threshold, was elicited by stimuli less than 60 dB above the hearing threshold in one or more frequencies. In several patients the reflex was elicited by stimuli with an intensity only 15–30 dB above the hearing threshold (Fig. 3).

Perstimulatory adaptation test (tone decay test) carried out in 3 or 4 frequencies in each ear was performed in all the 12 patients. The patient was presented a tone 5–10 dB above the hearing threshold and asked to hold his index finger up as long as he heard the tone. When the patient indicated that the tone disappeared, the intensity was increased in steps of 5–10 dB until he heard the tone again. This was continued until the

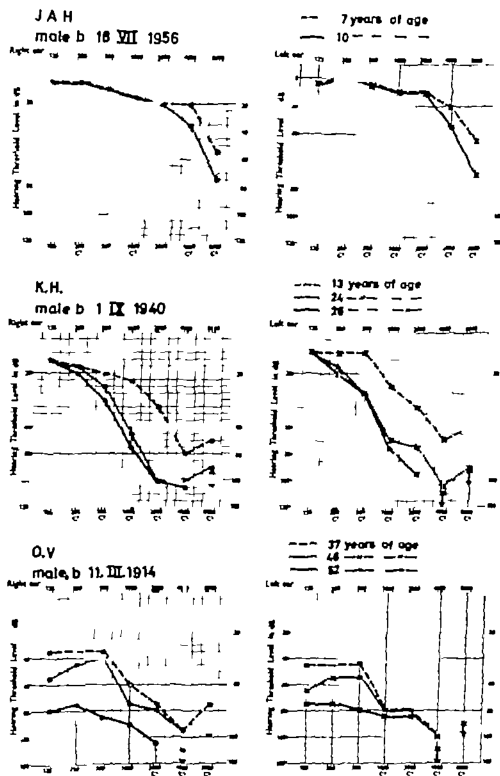


Fig. 2 Diff rent phases of the progressive hearing lo R pe ted di gram in 3 patients how the progression of th hearing loss in different g pe lods.

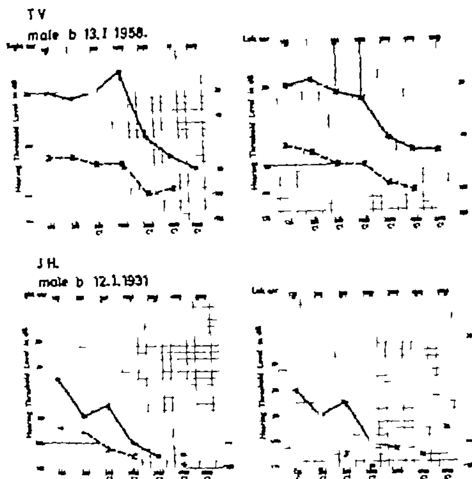


Fig. 3. Recruitment demonstrated in 2 patients by the Metz recruitment test. The stapedius muscle reflex (Z) is elicited by pure tone stimuli with intensity 10–15 dB above the hearing threshold.

patient could hear the tone continuously for 90 seconds, or until the maximum output of the audiometer was reached. Because of interfering tinnitus and/or lack of cooperation, the results of this tiresome and attention-demanding examination could be considered reliable in only 9 of the patients. In frequencies where the hearing loss was less than 50 dB there was no sign of pathological tone decay in any of the patients. The test was carried out in a total of 38 frequencies where the hearing loss was more than 50 dB. In 11 of these frequencies there was a threshold shift of 25 dB or more during the test. In some frequencies there was a threshold shift of 30–50 dB before the tone disappeared completely (Figs. 4 *a* and *b*).

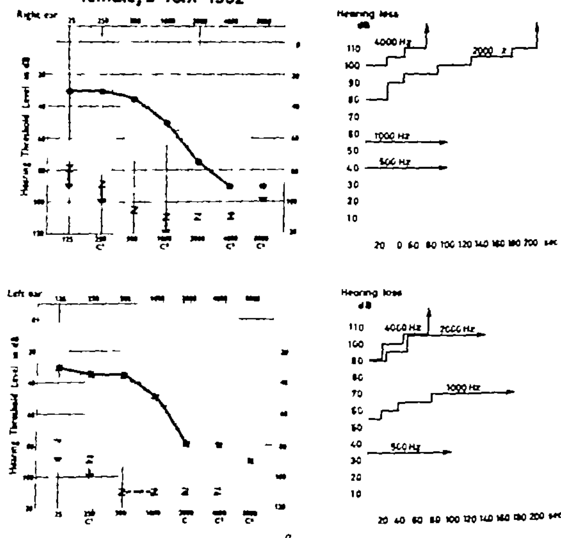
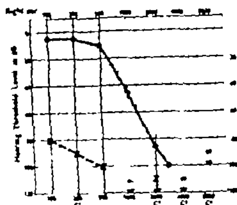


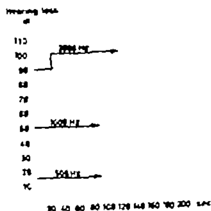
FIG. 4 *a* and *b*. Perstimulatory adaptation test (tone decay test) in two patients with typical hearing loss. A pathological threshold shift is demonstrated in several frequencies where the hearing loss is more than 50 dB.

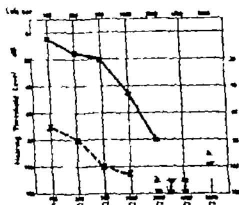
DISCUSSION

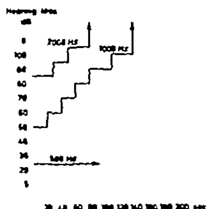
The present study of progressive perceptive hearing loss caused by autosomal dominant inheritance shows that the hearing loss follows a certain pattern in its development. This pattern is the same as the one described by Dolowitz & Stephens (1961) and by Huizing *et al.* (1966). It is therefore common not only to different members of the same family but also to different families carrying this disease.

Recruitment demonstrated by the Metz recruitment test points towards a degenerative lesion in the cochlea. Huizing *et al.* (1966) suggested that the experimentally established existence of two systems in the cochlea (Katsuki *et al.*, 1962; Smith & Sjöstrand, 1961), one for low frequencies and one for high frequencies, might explain the separate deterioration









b

of the high and low frequency hearing in these patients. If this theory is correct an identical development of the progressive hearing loss in different affected families must be predicted. The variable results of the tone decay test in the individual patient, depending on the frequency tested, show the importance of testing several frequencies in each ear before any definite conclusion is made. The pathological tone decay found in some frequencies where the hearing loss was more than 50 dB suggests an additional degenerative lesion in the more central auditory pathways. However several authors consider an abnormal auditory adaptation a phenomenon which also can be found in cases with a lesion exclusively in the cochlea (Hood 1955).

ACKNOWLEDGMENTS

I want to express my thanks to the district health nurses, Oddbjorg Rein, R.N. and Randi Asen, R.N. for their invaluable assistance in tracing the dif

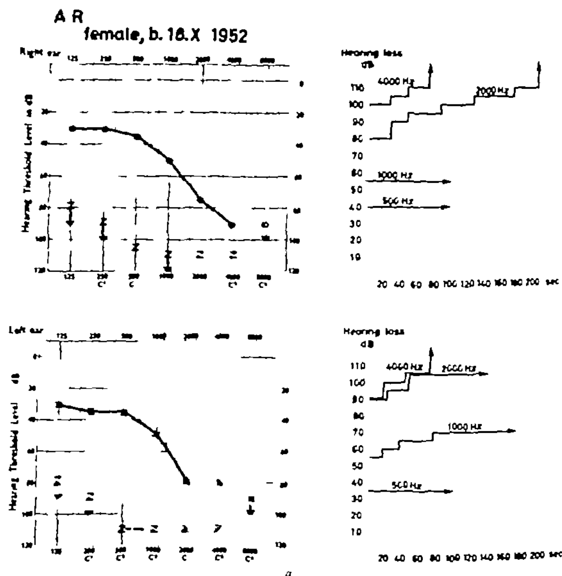


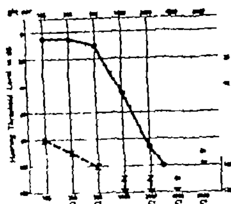
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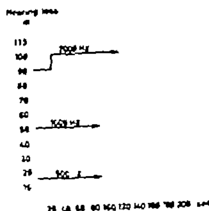
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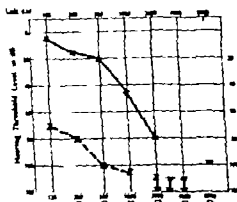
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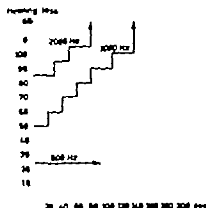
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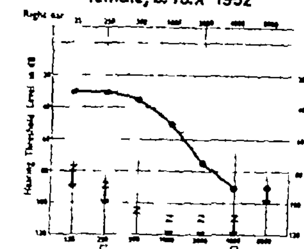


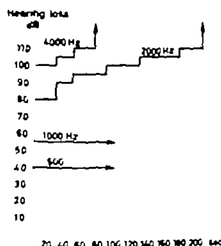
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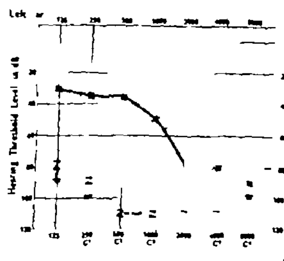
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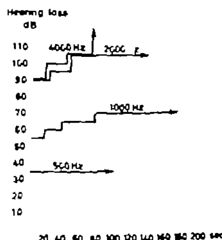


FIG. 4 *a* and *b*. Peristimulatory *adaptation test* (tone decay test) in two patients with typical *hearing loss*. A pathological threshold shift is demonstrated in several frequencies where the hearing loss is more than 60 dB

DISCUSSION

The present study of progressive perceptive hearing loss caused by autosomal dominant inheritance shows that the hearing loss follows a certain pattern in its development. This pattern is the same as the *one* described by Dolowitz & Stephens (1961) *and* by Huizing *et al.* (1966). It is therefore common not only to different members of the same family but also to different families carrying this disease.

Recruitment demonstrated by the Metz recruitment test points towards a degenerative lesion in *the* cochlea. Huizing *et al.* (1966) suggested that the experimentally established existence of two systems in the cochlea (Katsuki *et al.*, 1962; Smith & Sjöstrand, 1961) one for low frequencies, and one for high frequencies, might explain the separate deterioration

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INFLUENCE OF CONTACT CUES ON THE PERCEPTION OF THE OCULOGRAVIC ILLUSION[1]

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Measurements were made on five normal and five labyrinthine-defective men when they stood erect in a room while it was stationary and again when it was rotating. The procedure was designed to produce two situations for the normal men in which otolith and nonotolith information were synergistic and three others in which they were antagonistic. Perception of the visual horizontal during rotation was not systematically related to differences in head and body position nor were there significant differences between the normal and L-D men. The results show that nonotolith information predominates in this experimental situation.

The purpose of this study was to investigate the role of otolith and nonotolith gravireceptors in the perception of the visual horizontal in darkness when observers stood on a rotating platform. It was hoped that the results would shed some light on the contribution of the nonotolith gravireceptors in the perception of the visual horizontal in normal and labyrinthine-defective (L-D) men. It is well known that normal and L-D men show significant differences in such phenomena as counterrolling (Miller 1961), the oculogravic illusion (Graybiel, 1952; Graybiel & Clark, 1965) and their perception of motion on a parallel swing (Guedry, 1965). At the same time it is also well known that L-D men can compensate for the loss of vestibular function in certain situations. For example, Clark & Graybiel (1963) have shown that in a series of 30 successive settings to the postural vertical both normal and L-D men made systematic improvement. The normal men showed smaller average errors, but the differences were small, particularly after 15 trials, and were not statistically significant. Specifically, the present study compares the performance of normal and L-D men with various head and body positions to determine their influence on the perception of the visual horizontal.

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Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

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ZUSAMMENFASSUNG

In einer Familie bestehend aus 72 Mitgliedern hat man bei 12 Frauen und 13 Männern eine vererbliche zunehmende perzeptive Taubheit diagnostiziert. Die Vererbung ist autosomal dominant und völlig durchdringend Die Gehörabnahme entwickelt sich nach einem speziellen Muster es fängt im oberen Tonbereich an und betrifft später auch die tieferen Töne Nach Verwendung der Recruitment probe von Metz hat man in allen Fällen die untersucht worden sind einen Lautstärkeausgleich gefunden Die Hörermüdungsprobe (tone decay test) hat in den Tönen mit Gehörabnahme weniger als 50 dB normale Werte und in einigen Tönen mit grösserer Gehörabnahme eine pathologische Schwellenveränderung gezeigt Die audiologische Untersuchung weist darauf hin dass eine degenerative Schädigung der Schnecke und zusätzlich wenn die Gehörabnahme grösser ist eine mögliche Schädigung der mehr zentralen Strukturen vorliegt

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from the horizontal axis of the device itself The goggle was easily held in place by the observer and a flexible rubber fitting prevented light leaks under the operating conditions used. Three levels were used to monitor the alignment of the goggle apparatus, the observer s head and his body The first level was located on the goggle itself the second on a band over his head, and the third on his back

PROCEDURE

All measurements were made with observer standing with his head and body in one of five different positions with respect to gravity After the room had been maintained at a constant velocity for one minute, the posi tion of his head and body and the goggle were set by means of the levels. Each trial was begun by an experimenter who offset the line from the horizontal, and observer s task was merely to set it to the gravitational horizontal Three experimenters were required for every trial One observed the level on the observer's back to monitor his body position a second experimenter monitored the level on the head and on the goggle and offset the luminous line before each setting and the third made and recorded the readings. No setting was recorded unless the monitors were satisfied that the proper head and body positions were maintained within a half degree An attempt was made to make the readings promptly in all trials because three of the positions were somewhat uncomfortable to main tain for prolonged periods. Nevertheless, observer was permitted to take as much time as he felt he needed to make an accurate setting. The light was turned off while the line was offset. The observers made five successive settings to the horizontal for each of five conditions facing forward and then fiv additional settings facing backward, with an interval of several hours between the two series. The five combinations of head and body position were I Static settings were made with observer standing on the floor with head and body erect and with the room stationary II Observer mad settings to th visual horizontal with both head and body aligned with resultant force (RF) while h tood on the platform set at 20 and with the room rot ting to produce a change of direction of RF from gravity f 20 degrees. III This was the same as II except that the head and body were aligned with the force of gravity IV This was th same as II but the body was aligned with RF whil the head was aligned with gravity V This was also th same as I except that the body was aligned with gravity while the head was aligned with RF

RESULTS

For the purpose of analysis, all of the data during rotation were com puted as deviations from the mean of each observer's settings to gravitational horizontal under static conditions (Condition I) The mean of these

METHOD

Observers

Five normal and five deaf L-D observers were studied. The normal men were medical students who showed normal responses to caloric stimulation (McLeod & Meek, 1962) and to an ataxia test (Graybiel & Fregly 1966). The L-D observers had acquired their bilateral deafness in childhood as a sequelae of meningitis and showed abnormal responses to the caloric and ataxia tests. All of the men had had experience in making observations in rotating devices and with the goggle device used to measure the perception of the visual horizontal.

Apparatus

The experiment was conducted on the Coriolis Acceleration Platform a slow rotation room in which it is possible to rotate observers for prolonged periods. The room is a circular windowless room 20 feet in diameter and 10 feet high without central supporting members It has a direct motor drive and the capability of controlled angular accelerations at rates up to 15 degrees per second either in a clockwise or counterclockwise direction although in this experiment it rotated only counterclockwise. Angular velocities up to 35 rpm may be maintained with an accuracy of plus or minus one per cent It is capable of carrying a payload of about 9000 pounds, and up to ten persons may participate in an onboard experiment It is well instrumented and has provision for a wide variety of laboratory equipment and living facilities. The operations required in this experiment were well within the limits of the device

All of the observations were made with observer s head 7.5 feet from the center of rotation of the room and at a velocity of approximately 11 9 rpm counterclockwise This produced a change in the direction of resultant force of 20 degrees at the observer s head He stood facing the direction of rotation (and for a second series opposite the direction of rotation) on a platform tilted upward 20 degrees from the floor on the outboard side of the room As a result, when he stood erect he encountered no difficulty in standing, and the resultant force acted directly from head to feet Thus, during rotation he stood comfortably erect on the platform with his body weight slightly greater than normal

The observer s task was to set a collimated red luminous line to the perceived horizontal He viewed the luminous line in a self-contained apparatus mounted in a goggle which he held snugly in position before his eyes The apparatus consisted essentially of a luminous line which was viewed by the right eye only while the left eye was in complete darkness The luminous line could be rotated either clockwise or counterclockwise by means of a knurled knob which was easily reached by either the observer or the experimenter The digital readout was in degrees deviation

TABLE 2. *Analysis of variance summary table*

Source of variation	Sums of squares	df	Mean squares	F
Between subjects	90.9	9		
A Normal-L-D	8.8	1	8.6	1.10[a]
Subjects within groups	62.1	8	7.8	
Within groups	561.5	40		
B. Body position	317.8	4	79.5	11.9[b]
A × B	28.1	4	7.0	1.0[a]
Subjects × within groups	215.6	32	6.7	

[a] p 0.25. [b] p 0.01

Perception of the Visual Horizontal during Rotation

During rotation the mean settings of the perceived visual horizontal deviated systematically from the resultant horizontal for Conditions II to V. In each case (Table 1) this mean setting which varied from 4.0° to 8.5° was between the resultant horizontal and gravitational horizontal but much closer to the former. This means that the outboard segment of the line was set below the resultant horizontal. Specifically, both the normal and the L-D observers set the luminous line clockwise from the resultant horizontal when they faced forward and counterclockwise when they faced backward. All of these deviations were statistically significant from zero (for the normals $p < 0.001$ and for the L-Ds $p < 0.01$ for each comparison). It should also be noted that the L-D men showed a slightly greater variance (Table 1).

An additional analysis of the significance of the difference among the various combinations of head and body position during rotation revealed that for the normal men (Table 1) there were no significant differences among Conditions II to V ($p > 0.05$ for all comparisons). All of these settings deviated significantly from the static settings, but head and body position did not appear to be determining factors within the limits of this experiment. It should be noted in particular that the setting of the luminous line with head and body aligned with resultant force (Condition II) was no different from the setting when the head and body were aligned with the force of gravity in Condition III.

Similar results were found for the L-D men with two exceptions. There were no significant differences between Condition II and Conditions III to V nor between Condition III and IV ($p > 0.10$ in every case). There were, however, significant differences between Condition V and Conditions II and IV ($p < 0.01$ in each case). It should also be noted that the low mean performance of the L-D men was predominantly a result of the settings of one observer who set the line in the opposite sense from the others throughout his trials while he faced forward. It should also be noted that he had

TABLE 1

ESTIMATE OF THE GRAVITATIONAL (CONDITION I) OR GRAVITOINERTIAL (II TO V) HORIZONTAL MADE BY SETTING A LUMINOUS LINE IN THE DARK

CONDITION			I	II	III	IV	V
BODY POSITION							
DEVIATION FROM GRAVITY OR RESULTANT FORCE IN DEGREES	NORMAL MEN	MEAN	07	44	63	44	40
		SD	21	13	22	22	16
	L-D MEN	MEAN	02	66	60	85	38
		SD	16	32	28	28	29

static observations was considered to be his point-of subjective-horizontal for this particular experimental situation although the deviation of the point-of subjective-horizontal from the gravitational horizontal in each case was very small (Table 1) Therefore, all of the deviations in Conditions II to V are deviations from observer s subjective horizontal using the goggle device *rather than from gravity or resultant force*

An initial analysis of the data was made to determine whether the mean deviations of the settings while the observer faced forward were signifi cantly different from those when he faced backward Comparisons of these observations for all five conditions and for both groups of observers revealed no significant difference ($p > 0\ 05$ or *greater for all comparisons*) between these two sets of observations. Consequently the analysis of the data (Tables 1 and 2) is made completely on the basis of the mean of the observations while observer faced forward and backward

The combined data for the normal and L-D men and the five conditions (Table 1) were subjected to a two-way analysis of variance (Winer 1962) for repeated measures on the same elements, and the results are sum marized in Table 2 The analysis revealed no significant variation between the normal and the L D observers, but the F was significant for the five conditions The interaction between the two conditions was not significant, indicating that the profiles for the two groups have the same shape

Perception of the Visual Hori ontal under Static Conditions

When the data for the first and second series of observations (Condi tion I) were combined the normal men showed a mean deviation of 0 7 counterclockwise from the gravitational horizontal while the L D s had a mean deviation of only 0.2 clockwise Neither of these differed signifi cantly from zero ($p > 0\ 10$ in each case) Thus, both the normals and L D s can be said to set the line to the gravitational horizontal with this goggle device under static conditions with a very small insignificant error

5 *Observer* perceived his body as being tilted away from the horizontal floor of the room by his own effort whereas in the typical experiment on the oculogravic illusion he perceived the chair floor and his body to be tilted outboard.

6 In this study there was no pressure against the outboard side of his body as in the case of the supported, passive, apparent tilt.

The results of this experiment may be understood as a function of the complex, dynamic interaction of the many inputs from tactual receptors of the feet, kinesthetic receptors stimulated by the maintenance of bodily posture and perhaps from other proprioceptors In Condition III for normals, otolith information and the nonotolith information from the head and trunk were the same as in the typical experiment in which the oculogravic illusion is observed On the other hand, for both groups kinesthetic information in maintaining bodily posture was present as were tactual cues from the feet. Transient information was available from the semicircular canals at the time observer tilted his head or body Whereas in the situation in which the oculogravic illusion is observed there is apparent tilt of the observer the seat, and the floor In the present experiment the information is merely that observer has tilted his body The frame of reference for the L-D men in this experiment was, therefore, quite different with a resulting difference in the perception of the visual horizontal It is particularly worth noting that in Condition II where their head and body were aligned with resultant force, the point-of-subjective-horizontal was also rotated with the outboard segment downward. It is suggested that this may be explained by the fact that in this ambiguous situation the outboard shoulder had a somewhat greater weight which was disparate with respect to the other information regarding the horizontal

ZUSAMMENFASSUNG

Messungen wurden durchgeführt an fünf normalen und fünf labyrinthgeschädigten Männern, die in einem Raum, der 1mal still stand und 1mal rotierte, aufrecht standen. Der Versuch war so angelegt, dass für die normalen Männer zwei Situationen geschaffen wurden, in denen Otolith- und Nicht-Otolith-Information synergistisch waren und drei andere in denen sie antagonistisch waren Wahrnehmung der visuellen Horizontalen während der Rotation zeigte keine systematische Beziehung zu Unterschieden in Kopf und Körperstellung, auch ergaben sich keine signifikanten Unterschiede zwischen normalen und L-D Männern. Die Ergebnisse zeigen dass Nicht-Otolith-Information in dieser experimentellen Anordnung vorherrscht.

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considerable difficulty *maintaining* the appropriate body and head positions except when he stood with head and body aligned with resultant force (Condition II)

DISCUSSION

The results of the static observations are well known (Graybiel 1952 Graybiel & Clark 1965 Neal 1926) Both normal and L D men made very small errors which did not differ significantly from the gravitational horizontal It is of interest to note that the L-Ds actually showed a smaller constant error and a smaller variance than the normals. The static data also show that observations with the goggle device produce results which are similar to those found with other devices used to determine the accuracy of the perception of the visual horizontal

The results during rotation are clear-cut in showing no significant differences between normals and L D men in setting a luminous line to the horizontal under the conditions of this experiment The data suggest that contact information from the feet and kinesthetic information from the legs and body were adequate for the L-D observers to make the settings accurately i e they were able to use the complex information available in this dynamic situation where they were required to stand erect (Jones & Milsum 1965 Schone 1964) In the case of the normal observers, otolith information from the two head positions was integrated to produce a setting close to the resultant force The particular role played by each sensory process is not made clear by these data It is suggested however that kinesthetic cues are probably of special importance This notion is supported by a study of the E-phenomenon under conditions of supported and unsupported tilt (Werner *et al.*, 1951) By interpolation from the data, it was indicated that E phenomenon was about 3 5 for 20-degree tilts with the observer supported and that this increased to about 5 6 when he was required to maintain his own body position

It should be emphasized that the differences between this experiment and experiments in which normal and L D men show differences in the perception of the visual horizontal are related to the following importances in methodology

1 In this experiment the observer actively tilted his body from the waist and his head from the shoulders rather than being passively tilted

2 In the present experiment the observer was not supported in any way instead of being firmly supported in position

3 The observer s feet were firmly planted on the floor which was set at the resultant horizontal rather than sitting on a seat which was set at the gravitational horizontal

4 In the current experiment, observer viewed a collimated luminous line of light but he was required to hold it in his hands rather than having the device supported independently

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EFFECT OF CYANIDE ON COCHLEAR POTENTIALS

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Cochlear potentials we e recorded bef re, during and after perfusion of the scala tympani or scala vestibuli with Ringer's solution containing 20 millimoles of sodium cyanide. Cochlear potentials, including endocochlear potential (EP), were promptly depressed by the action of cyanid and a negati potential was observed in the scala media. The intracellular r sting potential within the organ of Corti was markedly de creased. Introduction of cyanide into the scala tympani was more effecti e than in the scala estibuli. Spontaneous recovery of responses was observed in most of the cases. The application of anodal polarization to the cochlea enhanced cochlear microphonics (CM) which had been depressed by cyanide. These data indicat that the cochlear partition is permeable to cyanide and confirm the iew that the negative potential in the anoxic scala media is essentially a depolarization potential of the hair cells in th organ of Corti.

INTRODUCTION

Cyanide is widely utilized as a metabolic inhibitor to induce anoxia in various tissues (Lorente de Nó, 1947, Wright 1947, Hodgkins & Keynes, 1954, 1955, Schoepfle *et al.* 1959, Schoepfle, 1963). The most significant effect of cyanide appears to be on the cytochromes and consequently the xygen cannot be utilized in the tissues. Cyanide blocks the transport sequence at oxidative phosphorylation stages and, reacting with the cytochromes, it prevents formation of ATP which is the principal compound upplying energy (Oser, 1965). As far as th cochlear end-organ is concerned, little is known about the effect of cyanide on the cochlear potentials. Davis *et al.* (1935) reported that the cochlear potentials, including EP, were promptly abolished by small doses of sodium cyanide injected into any one of the scalae. The work reported here was undertaken in order to explore more fully the effect of cyanide on the various cochlear potentials.

METHODS

Healthy guinea pigs anesthetized with pentobarbital sodium were used as experimental animals. When recording CM, summating potential (SP) and action potential of the auditory nerve (AP), the differential electrode

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free of HCO and PO was used in an attempt to insure maximal stability f Ca ion concentration and to prevent loss of cyanide from solution (Schoepfle *et al* 1930) The pH and the osmolarity of this solution were 9.5 and 380 mos/kg respectively

RESULTS

As control experiments, the scala tympani or scala vestibuli was perfused with modified Ringer's solution which contained *107 millimoles of* Na and the pH was adjusted to 9.5 by adding small and physiologically insignificant amounts of NaOH EP did not show any significant changes during or after the perfusion AP and CM did decrease their magnitude *gradually during perfusion of scala tympani. With 6000 cps tone bursts* of about 53 db above the just detectable threshold of CM, the depression of N was *70 to 80%* and *CM decreased to 85%* *at the end of the perfusion.* Both CM and AP recovered completely within 5 minutes after completion of the perfusion. The effect of perfusion of scala vestibuli with the control perfusate was slight and complete recovery of the response was observed within 3 minutes.

The perfusion of the scala tympani with NaCN solution was carried out under *the same conditions as the control. The introduction of cyanide into* the scala tympani resulted in dramatic changes in cochlear potentials. First of all EP began to drop 20 to 30 seconds after the onset of the perfusion. In 13 cases the average survival time of EP defined as the time

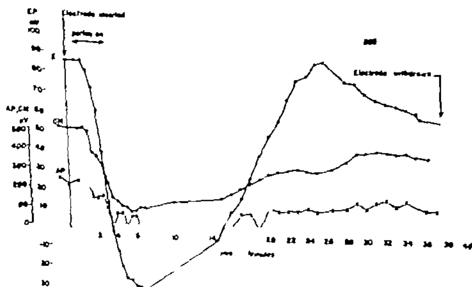


Fig. 1 Behavior of CM, AP N and EP during and after application of 60 millimoles of NaCN–Ringers solution to the scala tympani. Stimulus 6000 cps tone burst t approximately 53 dB above the CM pseudo-threshold.

technique was employed (Tasaki *et al.*, 1952) For measurement of EP a glass pipette electrode was inserted into the scala media through the spiral ligament and connected to an electrometer As a reference electrode a chloride-coated silver electrode was placed on intact neck muscles. The sound stimuli were tone bursts of moderate intensity between 6000 and 10 000 cps All these techniques have been fully described elsewhere (Butler *et al* 1960 Konishi *et al* 1961) When recording the dc potential in the organ of Corti, a superfine capillary microelectrode was used, which was filled with 3 moles of KCl solution. Its resistance ranged from 20 to 30 megohms. The electrode tip was brought near the inner edge of the basilar membrane after removing the round window membrane and the perilymph in the scala tympani. The direction of the electrode was adjusted so as to be perpendicular to the basilar membrane The microelectrode was then advanced toward the scala media with a hydraulic driver The microelectrode and the reference electrode in the neck were connected to an electrometer and permanent records were obtained by delivering the output of the electrometer to an oscillograph

The experimental method for applying the external anodal current to the hair cells was the same as that described by Tasaki *et al* (1952) and by us (in press)

The procedure for perfusion of the perilymphatic space was essentially the same as that described in our previous paper except for a difference in its rate (Konishi *et al* in press) A pair of small holes was made for perfusion of the scala tympani one in the scala tympani of the basal turn and the other in the scala vestibuli of the fourth turn of the cochlea. A glass pipette containing the perfusate was inserted into a hole in the basal turn and the hole in the upper turn served as an outlet For perfusion of the scala vestibuli a hole was made in the scala vestibuli of the basal turn to receive the perfusion pipette The location of holes for the perfusion was carefully selected so that the perfusate could pass the area where the electrical responses were recorded Since a distance of at least 1 mm was allowed between the perfusion pipette and recording electrodes, this length is sufficient to cover the electrical spread of ac and dc current along the cochlea (Tasaki, 1957 Konishi, unpublished data) When recording the dc potential in the organ of Corti the perfusion pipette was inserted into the scala tympani of the second turn and the round window served as an outlet as its membrane had been partially removed before the perfusion Approximately 10 microliters of the perfusate were introduced into the perilymphatic space for 3 to 5 minutes so as to avoid mechanical displacement of the basilar membrane which is reflected by sudden changes in dc potential in the scala media As a consequence the effective concentration of cyanide solution may be lower than the concentration actually introduced.

The perfusate used was 50 millimoles of sodium cyanide dissolved in Ringer's solution (mM NaCl 147 KCl 4 0 $CaCl_2$ 2 0) Ringer's solution

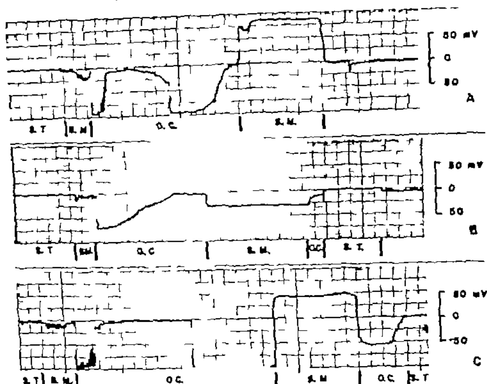


FIG. 2. Exploratio of the organ of Corti with microelectrode. Reading from left t right, the trace indicates the potentials recorded as the microelectrode was moved from the scala tympani t scala media. *Record A* Control before perf sion. *Record B* 1 mi t 30 seconds after the completion f perfusio of the scala tympa i with NaCN Ringer's solution. Record C 1 hour fter perfusion. Letters indicate locatio of the tip of the electrode *S.T B.M O.C* and *S.M* represent scala tympani, basilar membrane, orga of Corti or scala media respectiv ly

increase in magnitude when spontaneous recovery of CM could be obtained after the perfusion Fig 1 illustrates one example of response changes during and after perfusion of the scala tympani with NaCN solution.

The introduction of NaCN solution into the scala vestibuli resulted in similar changes in the cochlear potentials but its effectiveness was less than that of the perfusion of the scala tympani. The average survival time of EP and CM was 0 and 13 minutes respectively in 6 cases. The maximum negative pot ntial in the scala media after the perfusion averaged only 3 mV and ranged from 0 mV to −8 mV Three cases showed partial ecov ry of CM and AP after perfusion of the scala vestibuli and recovery of EP was obtained in all 6 cases. There was little difference in the spontaneou recovery of the responses between the perfusion of the scala tympani and that of the scala vestibuli Fig 2 shows the response decline during and subsequent to perfusion of the scala vestibuli.

In the third series of xperiments the dc potential of the organ of Corti

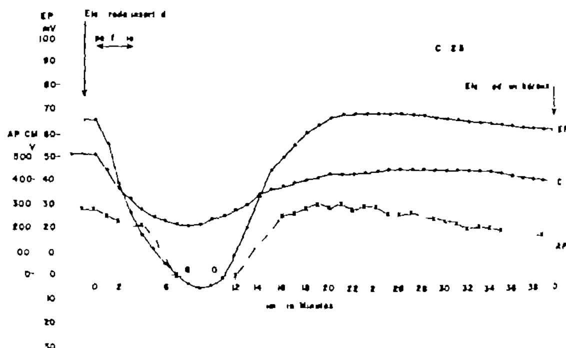


FIG. 2. An exampl f changes in CM, AP (N) and EP during a d after introduction of 50 millimol s of NaCN Ringer's solution into th scala vestibuli. Stimulus 6000 cps t n burst at about 55 dB abov CM pseudo-thresh ld.

required for EP to reach zero was 4 minutes 40 seconds. Upon reaching zero EP continued to decline, thus exhibiting a negative value This change took place when the reference electrode was placed either on the neck muscles or in the scala tympani of the basal turn The maximum negative value ranged from −3 mV to −35 mV and its average was −20 4 mV The time lapse required to reach a maximum negative potential varied considerably however in most cases it reached its maximum within 10 minutes after the perfusion started Both CM and AP were found to be reduced after the perfusion With 6000 cps tone bursts of about 55 db above the just detectable threshold of CM the average time required for CM to reach 50% of its original magnitude was about 2 minutes 30 seconds. The survival time of CM defined as the time elapsing before CM reached post mortem level ranged from 2 to 12 minutes and averaged 7 minutes 15 seconds The survival time of N_1 was shorter than that of CM and was found to average 4 minutes 30 seconds

All our animals, except one showed spontaneous recovery of EP after perfusion of the scala tympani with NaCN solution EP reappeared and about one third of our cases showed a temporary supernormality Four out of 13 cases did not show recovery of CM and AP Both CM and AP recovered only partially in 8 cases SP did not show consistent changes during or after the perfusion but the negative SP was increased during the initial period of the perfusion and the positive SP was often observed shortly after CM reached post mortem levels. The negative SP showed progressive

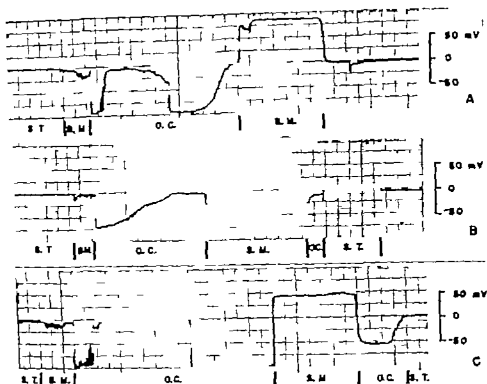


Fig 1. Exploratio of the org f Corti with microelectrode Reading from left to right, the trace ndicates the potentials recorded as the microelectrode was moved from the scala tympan to scala media. Record A Control before perfusi n. Record B 1 minute 30 seconds after the completion of perf sion of the scala tympani w th NaCN Ringer's solution. Record C 1 ho after perf ion. Letters indicate location f the tip of the lectrode. *S T* *B.M* *O C* and *S.M* represent scala tympani, basilar membrane, organ of Cort or scal media respectiv ly

increase in magnitude when spontaneous recovery of CM could be obtained after the perfusion Fig. 1 illustrates one example of response changes dur ing and ft r perfusion of the scala tympani with NaCN solution

The introduction f NaCN solution into the scala vestibuli resulted in similar changes in the cochlear potentials but its effectiveness was less than that of the perfusion of the scala tympani The average survival time of EP and CM was 9 and 13 minutes respectively in 6 cases. The maximum negativ potential in the scala media after the perfusion averaged only 5 mV and ranged from 0 mV to −8 mV Three cases showed partial recovery of CM and AP after perfusion of the scala vestibuli and reco ery of EP was obtained in all 6 cases. There was little difference in the spontaneous recovery of the responses between the perfusion of the scala tympani and that of the scala vestibuli. Fig. 2 shows the response decline during and subsequent to perfusion of the scala vestibuli.

In the third series f experiments the dc potential of the organ of Corti

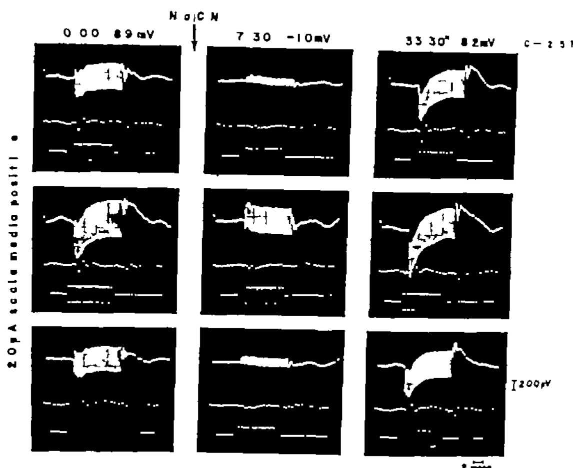


Fig. 4 Changes in cochlear potentials induced by a polarizing current flowing from scala media to scala tympani before and after introduction of NaCN into scala tympani Numbers in the uppermost line indicate time elapsed between onset of perfusion and application of the current those below show EP before the current was sent to the cochlea Photographs in the upper middle and lower rows were taken before during and after the application of current respectively In each photograph, the upper tracing shows CM, the middle one AP and the bottom one stimulus. Stimulus 9000 cps tone burst at about 50 dB above CM pseudo-threshold in normal condition.

was explored with a microelectrode when the negative dc potential in the scala media reached a plateau after introduction of NaCN into the scala tympani The exploration was carried out in rapid succession at two or three locations along the inner edge of the basilar membrane These successive recordings almost always fell within the range of ±5 mV In all successful cases the resting potential in the organ of Corti ranged from −80 to −100 mV before perfusion Its maximum depression after perfusion after perfusion of the scala tympani with NaCN varied considerably from −25 mV to −70 mV As shown in Fig 3 the dc resting potential in the organ of Corti was greatly depressed shortly after perfusion of the scala tympani with NaCN This depression was reversible when the negative dc potential in the scala media recovered spontaneously after the perfusion as shown in Fig 3

When the scala media electrode was connected to a source of direct current and the glass pipette electrode in the scala tympani to its sink, both CM and the negative SP showed an increase in amplitude in the normal condition. When the negative dc potential in the scala media reached a maximum after the perfusion of the scala tympani with NaCN solution, the application of the dc polarization current resulted in an enormous enhancement of CM as shown in Fig. 4. The rate of this increase in CM was greater in the anoxic condition than in the normal. The changes of CM were always reversible. AP did not show any noticeable increase when the current was applied about 10 minutes after completion of the perfusion.

DISCUSSION

There are accumulated data available showing that the cochlear potentials are highly dependent on oxygen supply (Wever *et al.*, 1949; Békésy, 1952; Davis *et al.*, 1955; Gisselsson, 1955; Tonndorf *et al.*, 1955; Davis, 1957; Tasaki, 1957; Fernández *et al.*, 1959; Konishi *et al.*, 1961). Also it has been demonstrated that prolonged exposure of nerve to cyanide produces a gradual decline in both the action potential and the resting potential (Schmidt *et al.*, 1931; Lorente de Nó, 1947; Wright, 1947). According to Hodgkin & Keynes (1955), NaCN inhibits active sodium extrusion which results in decrease of Na^+ efflux and K^+ influx. The inhibition of the metabolically linked sodium potassium exchange accounts for a loss of intracellular potassium. Therefore depression of the cochlear potentials by treatment with NaCN is to be expected.

The NaCN Ringer's solution was a sodium-rich hypertonic solution with a high pH. We examined the effects of these factors on cochlear potentials. Referring to these unpublished data, EP was found to endure hypertonicity and high pH of this perfusate and to be little affected by high Na concentration, although CM and AP, especially AP, were depressed temporarily (Konishi, unpublished data). Consequently the high pH and hypertonicity of this NaCN Ringer's solution do not seem to affect our results seriously.

The survival time of the cochlear potentials obtained in this present experiment is somewhat longer than that reported by us previously (Konishi *et al.*, 1961). It is possible that this discrepancy is due to the experimental conditions. Occlusion of the anterior inferior cerebellar artery eliminates the blood flow in the cochlea promptly and completely, whereas NaCN introduced into the perilymphatic space diffuses through the cochlear partition before it depresses the source of the cochlear potentials. Also the production of perilymph and leakage of the cerebrospinal fluid through the cochlear aqueduct cause dilution of NaCN Ringer's solution introduced into the perilymphatic space and this may account for spontaneous recovery of the cochlear potentials.

Among the various hypotheses put forward to explain the negative po-

tential in the anoxic scala media (Békésy 1952 Konishi *et al.*, 1961 Rice *et al* 1961 Honrubia *et al* 1965 Johnstone, 1965) Honrubia *et al* postulated that the negative potential in the asphyxiated scala media is contributed by accumulation of metabolites in the scala vestibuli. If this is the case NaCN introduced into the scala vestibuli would cause a larger negative potential in the scala media than that introduced into the scala tympani. However our data demonstrate that the negative potential in the scala media is produced more effectively by the introduction of NaCN into the scala tympani If the stria vascularis is the source of the negative potential in the anoxic scala media as one of us speculated (Konishi *et al* 1961) then the degree of the action of NaCN on the stria vascularis would be the same regardless of which scala was perfused with NaCN

We proposed in our previous paper (Konishi *et al* in press) that the negative dc potential in the anoxic scala media represents an anoxic depolarization potential of the hair cells. Further evidence to support this view is the decrease of the negative potential in the organ of Corti after introduction of NaCN into the scala tympani Butler (1965) reported that the resting potential in the organ of Corti decreased after asphyxia and he pointed out that this negative potential is of extracellular origin The tip diameter of the glass pipette electrode used in our experiments was far less than that he used When the resistance of the electrode changed after the penetration, indicating damage to its tip the data were discarded Also the basilar membrane was directly visualized after careful removal of the perilymph so that the microelectrode penetrated its inner edge Therefore we can safely assume that the negative potential recorded during the penetration of the cochlear partition is of intracellular origin. It appears from these data that the cellular elements in the organ of Corti including the hair cells, were depolarized by the action of NaCN Similar findings were reported by Lorente de Nó (1947) that NaCN in high concentration produces a depolarization of nerve fibers in about the same manner as does oxygen lack

The enhancement of CM by anodal polarization observed after treatment with NaCN is in line with our previous report (Konishi *et al* in press) Schoepfle *et al* (1959) reported that strong hyperpolarization is effective in overcoming sodium inactivation in the frog single nerve treated with NaCN Ringer's solution Lorente de Nó (1947) also reported the ability of anodal current to increase the polarization of the membrane of anoxic nerve Tasaki *et al* (1952) found an increase of CM and AP when anodal current was applied to the organ of Corti and concluded that the modifications of CM and AP by anodal polarization might be due to changes in the resting potential of the cells of the organ of Corti One possible explanation of our results is the fact that anodal polarization applied to the organ of Corti causes repolarization of the hair bearing ends of the hair cells which have been depolarized by the action of NaCN It appears from the results in the present study that the cochlear partition is permeable to cyanide

and that local application of cyanide causes changes in the cochlear poten tials similar to those observed in other tissues (in nerve fibers, Lorente de Nó, 1947 Wright, 1947 Hodgkins *et al* 1955 Schoepfle, 1959 and in smooth muscle fibers, Guttman, 1939)

CONCLUSION

A study has been made f the effect of NaCN in the perilymph on the cochlear pot ntials in guinea pigs.

When th perilymph was replaced with Ringer' solution containing 30 millimoles of NaCN CM and AP were promptly depressed.

The endolymph showed n gative pot ntial in respect to the perilymph after treatment with NaCN

The intracellular resting potential within the organ of Corti was markedly depressed by the action of NaCN

Cochlear potentials showed sponta eous reco ery in most cases.

Application of anodal polarization enhanced CM which had been depressed by NaCN

It i concluded from these data that the cochlear partition is permeable to NaCN and that the negati potential in the an l scala media i essentially a depolarization potential of the hair cells in the organ of Corti.

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ZUSAMMENFASSUNG

Cochleare l tentiale wurden registriert or wahrend und nach Perfusion de Scala tympan oder der Scala est buli mit Ringers Lösung, di 0 Millimole N triumcyanid enthi lt. Cochle re P tential Inschliessli h endocochleare Potentiale (EP) wurd n sofort durch die Wirk ng des Cyanid geh mmt und ein negat es Pot ntial wurd in der Scala media beobachtet. D s intraz llulare R hepotential innerhalb des Cortischen Orga wurd stark ermi dert. Die Einfuhrung n Cy nid n di Scala tympani war von grösserer Wirkung al in di Scala estibuli. Spontane Ru kkeh de *Reaktion n wurd in den meist n* F llen beobacht t Anodale Polarisat on der Cochle verstarkte cochleare Microphonie (CM) ie durch Cya id t rdruckt worden w r Diese Resultate zeige dass die cochleare Trennungswand permeabel ist für Cyanid und bestätigen die Ansicht, dass da negati e Pote tial in der an xischen Scala media im w sent lichen ein Depolarisations-Potential d *Haarzellen des Cortisch n Organs ist.*

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ISOLATED PSYCHOGENIC PALATAL MYOCLONUS AS A CAUSE OF OBJECTIVE TINNITUS

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The authors draw attention to objective tinnitus due to palatal myoclonus when occurring as a solitary complaint. The belief is expressed that in such cases psychiatric disorder *is the underlying cause. The need for* psychiatric treatment in these cases is stressed. Contrarily, palatal myoclonus as a component of neurological syndromes is attributed to organic lesions of the central nervous system. These conclusions are based on five illustrative cases and a review of the literature. Any classification of the tinnitus has to be extended to include subdivisions of palatal myoclonus into psychogenic and organic varieties as distinct categories.

Objective (vibratory) tinnitus is, relatively, a rare condition and represents only a small proportion of cases suffering from noise in the ears. In spite of its rarity this is a well known entity in which the sound heard by the patient can, under certain conditions, also be perceived by the examiner (Pulec & Simonton, 1961; Graham, 1965; Wengraf, 1967). The diagnosis is simple and is made either by auscultation with a stethoscope, or by *listening through an auditory tube connecting* the patient's and the examiner's ears. Recording of the objective tinnitus is possible using a phonocardiograph, as described by Engström & Graf (1950, 1952) and Wengraf (1967).

Etiologically the objective tinnitus is divided into two distinct groups. First, apparently the minority group where the noise is due to vascular pathology (Engström & Graf, 1950, 1952; Bonnal & Legré, 1960; Wengraf, 1967). The second, larger group where the tinnitus is caused by clonus of the palatal and pharyngeal muscles. Several different causes of myoclonus of palate have been described (Björk, 1954; Pulec & Simonton, 1961; Wengraf, 1967).

In this paper we present five cases, where objective tinnitus due to myoclonus appeared as the only complaint. In all of them, psychogenic disorders were firmly found to be the underlying cause.

It is our purpose to propose that when palatal myoclonus appears as the solitary symptom, it is always of psychogenic origin.

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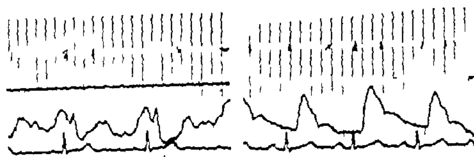


Fig. 1 F n. 2

Fig. 1 Phonographic recording of objecti ti nit due t palat l myoclon s. The upper tracing represent phonocardiogram. The next one recording of the tinnit s. Below jugular nous pressure At th bott m, E.K.G recording. No relationship w th ny manifestatio of cardiac acti ity

Fig. 2. Four tracings a abov Intensi ty of palatal myoclonus during 1 lsal a maneuver

Case 3

A 37 year-old married female, mother of 3 children presented herself with complaints of a rhythmic, incessant noise in her left nostril and left maxillary area. The noise could be heard clearly at a distance of approximately *one meter* *This cephalic murmur* was heard with a stethoscope *over the left maxilla, but could be heard neither in the ear nor over the* mastoid. Myoclonus of the soft palate was clearly seen both with the mouth open and through the nose The psychiatric investigation revealed that in addition to the ppearance of tinnitus, the patient offered multiple complaints, *mainly in the genital and urological systems At the conclusion of the* psychiatric investigation compulsive neurosis with conversive reac tions was diagnosed As in other cases, the tinnitus was regarded as a somatic expression.

Case 4

An 18-year-old male ppeared *because of a disturbing clicking tinnitus* in both ears, which was great r in the right side On examination eardrums appeared normal and audiometry revealed perfect hearing The radiography revealed normal temporal bones.

The clicking sound in both ears could be heard with the aid of the auditory tube which was *louder on the right side The sound* was not synchronous with *the pulse and did not change it* character with head movements. It could be stopped when the patient opened his mouth widely but on slight opening palatal myoclonus was observed. Neurological examination did not reveal deviations *from the norm*

According to psychiatric *examination the patient faced* a severe conflict

Case Reports

Case 1

A 27 year-old married male First examined in our outpatient clinic seven years after the onset of tinnitus in his left ear The history revealed that during those years he was examined by several physicians and hospitalized in different medical institutions. None of the treatments he underwent stopped or even changed the nature of the sound The otoscopic findings were normal as well as the audiogram and X rays of temporal bones

The patient's claim that the sound could be heard by the examiner proved to be correct. When connected to patient's ear a clicking regular sound not synchronised with the pulse, was heard The bruit could not be heard on auscultation over the mastoid and was influenced neither by head movements nor by pressure on the carotid artery The sound could be stopped temporarily by wide opening of the mouth and could change its character and become bitonal in a Valsalva maneuver The sound and its bitonality in a Valsalva maneuver were well demonstrated on recording with the phonocardiograph (Figs. 1 and 2)

Repeated investigations revealed rhythmic contractions of the soft palate corresponding to myoclonus.

The patient's behaviour and personality were suggestive of psychogenic disorders He was referred for a psychiatric evaluation which established —beyond any doubt—schizophrenia with an obvious paranoid pattern The myoclonus was interpreted as a somatisation of a compulsive defence mechanism We were advised against any mechanic therapeutic attempts to eliminate the tinnitus, so as not to precipitate an aggravation of his psychiatric disorder He remained under psychiatric care

Case 2

A 65 year-old man was seen in the E N T clinic because of a troublesome clicking sound in his left ear which appeared three years prior to the examination The eardrums, as well as the other E N T organs, were normal The audiometry revealed bilateral equal high tone hearing loss of about 35 dB interpreted as presbyacusis A clicking rhythmic sound could be heard when connected with patient's left ear It could be stopped voluntarily but reappeared spontaneously shortly thereafter When myoclonus of the soft palate was found the patient was referred for psychiatric evaluation The investigation revealed that the onset of the tinnitus coincided with a severe traumatic experience (sudden death of several members of his family) which caused loneliness, retirement and general depression. It was concluded that the myoclonus represented a compulsive tic due to tension and depression He remained under psychiatric care

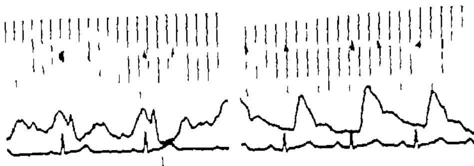


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Case 2

A 65 year-old man was seen in the E.N T clinic because of a troublesome clicking sound in his left ear which appeared three years prior to the examination The eardrums, as well as the other E N T organs, were normal The audiometry revealed bilateral equal high tone hearing loss of about 35 dB interpreted as presbyacusis A clicking rhythmic sound could be heard when connected with patient s left ear It could be stopped voluntarily but reappeared spontaneously shortly thereafter When myoclonus of the soft palate was found the patient was referred for psychiatric evaluation The investigation revealed that the onset of the tinnitus coincided with a severe traumatic experience (sudden death of several members of his family) which caused loneliness, retirement and general depression It was concluded that the myoclonus represented a compulsive tic due to tension and depression He remained under psychiatric care

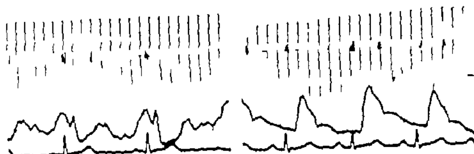


Fig 1 Fig. 2.

Fig. 1 Phonographic recording of objectiv tinnitus due t palatal myoclonus. The upper trac g represents phonocardiogram. The next one, recording of the tin itus. Below jugal enous pressure. At the bottom, E.K.G recording Y relationship with any manifestatio f cardiac activity

Fig. 2. Fou tracings as abo e. Rhonal ty of palatal myoclonus during Valsal maneu er

Case 3

A 37 year-old married female, mother of 3 children, presented herself with complaints of a rhythmic, incessant noise in her left nostril and left maxillary area. The noise could be heard clearly at a distance of approximately one meter This cephalic murmur was heard with a stethoscope er the left maxilla, but could be heard neither in the ear nor over the mast id Myoclonus of the soft palate was clearly seen both with the mouth open and through the nose The psychiatric investigation revealed that in addition to the appearance of tinnitus, the patient offered multiple com plaints, mainly in the genital and urological systems. At the conclusion of the psychiatric investigation compulsive neurosis with conversive reac tions wa diagnosed As in other cases, the tinnitus was regarded as a *somatic expression.*

Case 4

An 18-year-old male appeared because of a disturbing clicking tinnitus in both ears, which was greater in the right side On examination eardrums appeared ormal and audiometry revealed perfect hearing. The radiography re ealed normal t mporal bones.

The clicking sound in both ears could be heard with the aid of the *auditory tube* which was louder on the right side The sound was not synchronous with the pulse and did not change its character with head mo ements. It could be stopped when the patient opened his mouth widely but on slight pening palatal myoclonus was observed Neurological examination did not reveal deviations from the norm

According to psychiatric xamin tion th patient faced a severe conflict

with his father and the palatal myoclonus represented a neurotic reaction as a flight into disease He was advised to receive psychiatric treatment.

Case 5

A 19-year-old female presented herself in the outpatient department with a complaint of a noise in the head of more than a year s duration The onset of this complaint coincided with her father s sudden death The father himself had suffered from facial tic and chronic coryza. This cephalic murmur' could be heard from a distance of about one meter It had a clicking character not synchronous with the pulse. Palatal myoclonus was clearly seen the contractions being synchronous with the clicking sound

There was nothing abnormal discovered on E.N T examination hearing was normal as well as X rays of sinuses and mastoids.

A psychiatric examination revealed an anxiety neurosis with conversion symptoms, aggravated by the death of the father The patient was referred for further psychiatric treatment

DISCUSSION

The differential diagnosis between the objective tinnitus of vascular origin and that due to palatal myoclonus is based mainly on the character of the noise In the first type the sound is murmur like synchronous with the heart beat and it may change when the carotid artery is compressed. In palatal myoclonus, on the other hand there is a characteristic click which bears no relation to the pulse Its quality may be altered by activating the pharyngeal muscles The differences between these two groups may be clearly demonstrated by means of phonography (Figs. 1 and 3)

The cause of palatal myoclonus has been attributed to various lesions, among them vascular pathology multiple sclerosis, aneurysm or vertebral artery different tumors involving the brain stem or cerebellum and apoplexy (Bjork 1954 Parker 1956 Pulec & Simonton 1961) On the other hand non-organic disturbances, such as emotional conflicts, neurasthenia and neurosis have also been incriminated (Bjork 1954 Pulec & Simonton 1961)

Palatal myoclonus has been described in association with different neurological symptoms, such as hemiplegia nystagmus facial paresis, incoordination of movements, diplopia etc (Nathanson 1956) Even though it played only a minor rôle within much larger neurological syndromes, it has been noted for its persistency The click in these cases was heard uninterruptedly even in sleep anesthesia and in terminal coma

As stated by Nathanson (1956) some of these reported cases were examined post mortem and it was found that the primary pathology was located in the cerebellar hemisphere and was associated with secondary retrograde changes in the opposite inferior olive Myoclonic retraction of

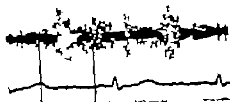
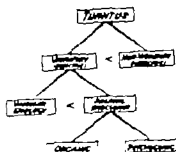



FIG. 3. Phonographic recording of objecti ti nitus of ascular origin. A short case

FIG. 4. Diagrammatic representation of classific tion of ti itus.

th palate has been experimentally produced in monkeys by electric stimulation in the region of the inferior olive (Weinstein & Bender 1943)

These observations warrant the conclusion that when myoclonus of the palate appears within broader neurological complex, it is caused by an organic disease Palatal myoclonus, when it appears as a solitary symptom, is of entirely different character In all our cases, the patients were able to control it to a certain degree In most instances it could be interrupted by opening of the mouth. The disease did not progress (in contrast to the evolutive character in the former group) and no additional symptoms appeared, even though the condition was in the majority of cases of long luration This point has been demonstrated also by other authors (Björk, 1954 Pulec & Simonton 1961) Heller (1962) cites a case of more than 20 years duration

In all our cases, an underlying psychiatric disease was firmly established The myoclonus was attributed to a tic, although the psychiatric entities w re different (schizophrenia, d pressive state, conversion reaction, anxiety neurosis, etc) In some cases an emotional trauma triggered the appearance f th tic (in two instances death of relatives) Furthermore on reviewing the lit rature it was noted that all cases reported as solitary myoclonus had n underlying emotional disturbance and most of them were described a a tic (Schwartz, 1948 Bjork, 1954 Pulec & Simonton, 1961 Heller 1962

CONCLUSION

In iew of these considerations it may be concluded that, whereas myoclonus participating in neurc logical syndrome is of organic origin, when it appe rs as a solitary phen menon, it is always of *psychogenic nature* In these cases it i mandatory to refer the patient for psychiatric evaluation and treatment N it mpla t mechanical interference with the tic should be undertaken, so s not to disturb the patient s delicate emotional balance and precipitate a deterioration of psychiatric condition.

The place of psychogenic myoclonus in the wider constellation of tinnitus of all types is indicated by the classification offered (Fig 4)

ACKNOWLEDGMENTS

The authors express their gratitude to Dr S Kulcsar Head of Psychiatric department for his guidance and instruction in evaluation of the psychiatric aspects. We are greatly indebted to Dr J Kraus, senior cardiologist, Heart Institute, Tel Hashomer Hospital for his contribution in performing and interpreting phonographic recordings

ZUSAMMENFASSUNG

Die Autoren besprechen in dieser Arbeit den objektiven Tinnitus, der durch Myoclonus des weichen Gaumens hervorgerufen wird, wenn dieser als Einzelsymptom besteht Es wird angenommen, dass eine psychiatrische Störung der ätiologische Faktor ist Die Notwendigkeit einer psychiatrischen Behandlung wird betont Andererseits ist der Myoclonus des weichen Gaumens als Komponente neurologischer Syndrome mit organischen Läsionen des ZNS verbunden. Fünf Fälle dienen als illustrative Beispiele der hier angeführten Zusammenhänge Die Besprechung der einschlägigen Literatur wird in diesem Sinne interpretiert. Die Autoren schlagen eine Unterteilung des Myoclonus des weichen Gaumens in eine psychogene oder organische Form als unterschiedliche Kategorien vor

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OLFACTORY ESTHESIONEUROMA

V KOLZE

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A case of olfa tory esthesioneuroma is reported with special reference to the histogenesis f this unusual nasal tumor The urinary excretion f 3-metho y-4-hydroxymandelic acid was found to be well within the range of normality and this is regarded as additional, if indirect, evi dence for the iew that the tumor is of olfactory epith lial origin.

Olfactory esthesioneuroma is an unusual neurogenic tumor of the nasal fossa. Berger t al. reported the first case in 1924 and called it "esthésio-neuroépithéliome olfactif" and considered the olfactory mucosa the site of origin. Two years later Berger & Coutard (1926) described a histologically slightly different tumor and termed it "esthésioneurocytome olfactif" They proposed olfactory esthesioneuroma" as a generic term which would include different histological subtypes. This term has been used by a few authors, but the designation olfactory esthesioneuroblastoma" is more common. Unfortunately this last term is also used in microscopical classification.

Only about 100 cases have been reported in the literature, but the tumor I probably not quite so rare as McCormack & Harris (1955) reported 3 cases ut of 80 nasal tumors and Obert *et al* (1960) found 8 cases in a ystematic retrospective study of 504 selected cases of intranasal neoplasms.

Case Report

The patient a woman 68 years old, was first seen in October 1966. The sympt ms were constant, left nasal obstruction, nasal discharge and prominence of the left eye of 6 weeks duration. In addition, she had suf fered from intermittent nasal obstruction and slight frontal headaches 6 months previously Since 1053 a hypertension had been known and treated.

On examination a grey easily bleeding tumor was seen, filling the whole left nasal fossa. No tumor was f und in the nasopharynx. The left eye was protruding with limitation of eye movement and on pressure a retrobulbar resi tance was f lt Sinus roentg nograms, including tomograms, revealed a soft tissue density of the left nasal cavity clouding of the left-sided sinuses and destruction of the orbital and cribriform plate of the ethmoid bone N cervical or pulmonary metastases were found. The urine was analysed for 3-meth xy-4-hydroxymandelic acid (VMA) and was found to

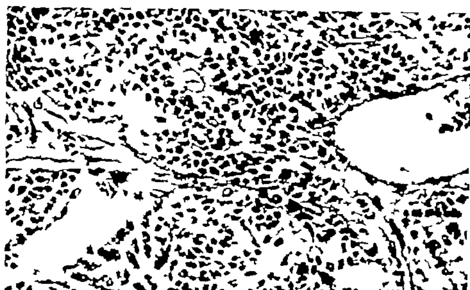


Fig. 1 Olfactory esthesioneuroepithelioma. Hematoxylin-eosin. × 100

contain 3.5 mg VMA/24 hours compared with the normal value 2–8 mg/24 hours. ESR 10 mm/hour and the blood pressure 225/120

Histological examination of biopsy specimen was performed by J V Thorborg M D The tumor was covered by a layer of loose connective tissue which extended into the tumor dividing it into compact cell groups. The majority of the tumor cells were small with sparse cytoplasm and polymorphous nuclei (Fig 1) There were numerous mitotic figures. In all parts of the cellular tumor tissue there were typical true rosettes, formed by more or less cylindrical cells around a central lumen containing a homogenous or granular substance (Fig 2) This substance and parts of a few of the marginal cells were PAS positive and also stained by Alcian Blue There were transitional forms between the small anaplastic and the epithelial cells Silver impregnation (Bielschowsky) demonstrated the existence of fibrils, mostly in the stroma no connection between these fibrils and the cytoplasm of the tumor cells could be seen The tumor was highly vascular and a few tumor emboli were visible in the thin walled blood vessels Diagnosis Olfactory esthesioneuroepithelioma

The tumor was considered inoperable and the patient was transferred to the Radium Centre Aarhus where she was treated with cobalt 60 teletherapy On completion of therapy no gross mass was visible in the nose but there was still a retrobulbar resistance, which had decreased by April 1967 when the patient was last examined

Pathology of Olfactory Esthesioneuroma

Macroscopically the tumor usually is a polypoid grey red easily bleeding lesion located high in the nasal fossa but the gross appearance varies, and



Fig. 2. Olfactory esthesioneuroepithelioma, true rosette. Hemat xylin-eosin. ×400.

the diagnosis is based on microscopical examination. Histologically the tumor is subdivided according to the presence or absence of rosettes. *The esthesioneuroepithelioma* is composed of epithelial as well as neural elements. Some of the tumor cells are cylindrical and grouped around a central cavity forming true rosettes, the so-called "rosettes pseudoglandulaires". The lumen is empty or contains an amorphous substance—often periodic acid-Schiff positive as in the present case—interpreted as cellular debris, and not as a true secretion product. The neural elements are fibrils and small lymphocytoid tumor cells (esthesioneurocytes) arranged in compact groups. In the *esthesioneurocytoma* the tumor cells are esthesioneurocytes and there are no true rosettes. A third type characterized by pseudorosettes (*a circle of cells around a central area containing fibrils*) has been described as the *esthesioneuroblastoma*. This type is ill-defined. The cells of the pseudorosettes do not differ from the other tumor cells, as in true rosettes, and it is often a question of interpretation how to define pseudorosettes. McCormack & Harris (1955) found no pseudorosettes in metastases from an esthesioneuroblastoma, although metastases otherwise are considered identical to the primary tumor (Gerard-Marchant & Micheau, 1965). The last two types lack epithelial differentiation and contain only neural elements, and some authors (e.g. Mendeloff 1957) prefer to consider these types as one group. Other authors (Becker & Jacox, 1964; Crahne 1965) have found no reason for making subdivisions.

Errors in microscopical diagnosis are common. The tumor is often diagnosed as an anaplastic carcinoma or a lymphosarcoma, but has also to be distinguished from other *small-cell neoplasms*. *Obert et al.* (1960) considered the presence of fibrils essential in the diagnosis, but fibrils are not always possible to demonstrate (Mendeloff 1957, Hutter *et al.* 1963). The olfactory esthesioneuroma possesses further some points of resemblance to the retinoblastoma and the sympathicoblastoma.

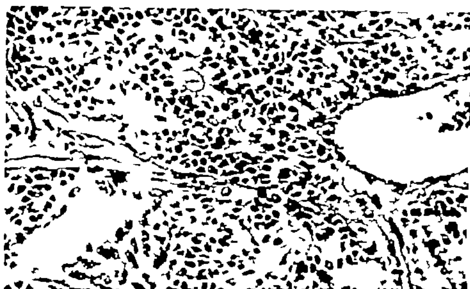


FIG 1 Olfactory esthesion uroepithelioma Hematoxylin-eosi ×300

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Theories of Histogenesis

It is generally accepted that the tumor arises independently of the central nervous system The olfactory epithelium probably is the site of origin as almost all olfactory esthesioneuromas originate from the upper part of the nasal cavity (Obert *et al.*, 1960) and the histological picture of epithelial and neural components points in the same direction The rosettes are supposed to be derived from the supporting cells and the esthesioneurocytes from the nerve cells of the olfactory epithelium A few esthesioneuromas are located in the maxillary sinus or the nasopharynx (Piquet 1950 Church & Uhler 1959 King, 1959 Mashberg *et al* 1960) and may possibly have been developed from displaced cells of the ectodermal olfactory placodes during the embryonic stage

A few cases of this tumor have been published as sympathicoblastomas on account of the similarity of microscopical features, and Escat (1931) considered the sphenopalatine ganglion as the origin, but if so, most esthesioneuromas should be localized in the nasopharynx Besides, there is an important clinical difference between sympathicoblastoma and ol factory esthesioneuroma as the former tumor is highly malignant and occurs almost exclusively in infancy and early childhood whereas the latter is a relatively benign lesion of the adult The urinary excretion of 3-methoxy-4-hydroxymandelic acid (VMA) which is the chief breakdown product of catecholamines, is often increased in cases of tumors of the symphathetic nervous tissue In the present case the urinary excretion of VMA was found to lie within the normal range The fact of VMA being normal could be taken as support for the view that the tumor is one of olfactory epithelial origin The blood pressure was elevated, probably due to essential hypertension and not because of production of catecholamines in the tumor Normal blood pressure is mentioned by some authors (Früh ling & Wild, 1954 Mashberg *et al.*, 1960)

Other suggested origins are the organ of Jacobson and the ganglion Loci of the terminal nerve but these are not consistent with the usual localization of the olfactory esthesioneuromas

Symptomatology

The olfactory esthesioneuroma occurs predominantly in adults, with the greatest frequency in the age group ten to forty years The youngest reported patient was a child nine years old and the oldest seventy nine No great differential sex incidence has been established. The symptoms, which are non specific begin with unilateral nasal obstruction, frequent epistaxis and nasal dischar less often with excessive lacrimation or anosmia When the tumor becomes locally invasive there may be unilateral ex ophthalmos diplopia, swelling of the root of the nose or headaches Sinu sitis, following blocking of the natural ostia, may cause the headache The

neoplasm may grow through the cribriform plate with secondary invasion of the brain, not necessarily giving cerebral symptoms. The tumor is usually slow growing and metastases occur only in 20 per cent of the cases, first in the cervical lymphnodes later in lungs, bones, and seldom in the spinal cord through the cerebrospinal fluid (Riemenschneider & Prior 1958) Roentgenologic examinations are of value in estimating the extension of the tumor Tingwald (1966) used mercury 203 scintigrams in the diagnosis of brain metastases.

Treatment and Prognosis

The tumor is usually radiosensitive and irradiation ought to be part of the treatment. Some authors consider the esthesioneurocytoma less radiosensitive than the esthesioneuroepithelioma which was also observed by Berger *et al* in the two cases at present this distinction is not sufficiently confirmed. A few cases were radioresistent (Becker & Jacox, 1964 Fitz Hugh *et al* 1965 Grahne, 1965) Radical surgery may be undertaken, but is often impossible. Experience with cytostatic therapy is scarce (Mendeloff 1957 Becker & Jacox, 1964 Grahne, 1965 Tingwald, 1966) but this treatment has been of some palliative value. At present the treatment to be preferred seems to be local excision, followed by radiation therapy

Skolnik et al (1966) found 50 patients in the literature followed up for more than five years. The five years survival was 52 per cent. Through treatments with surgery irradiation and combined therapy the five years survival *percentage was 64 38, and 50, respectively* values which probably reflect the effect of the tumor extension on the choice of treatment Some authors (McCormack & Harris, 1955 Gerard Marchant & Micheau, 1965) found a relationship between the histological picture and the prognosis, but no consistent relationship has as yet been convincingly established

ZUSAMMENFASSUNG

Ein Fall von seltenem Nasentumor Aesthesioneurom des Olfactorius, wird beschrieben, mit speziellem Hinblick auf die Histogenese. Die Ausscheidung im Urin von 3-Methoxy-4-Hydroxy-Mandelsäure ist normal geblieben was die Auffassung der Riechschleimhaut als Ursprungsort des Tumors unterstützt.

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Theories of Histogenesis

It is generally accepted that the tumor arises independently of the central nervous system. The olfactory epithelium probably is the site of origin as almost all olfactory esthesioneuromas originate from the upper part of the nasal cavity (Obert *et al.*, 1960) and the histological picture of epithelial and neural components points in the same direction. The rosettes are supposed to be derived from the supporting cells and the esthesioneurocytes from the nerve cells of the olfactory epithelium. A few esthesioneuromas are located in the maxillary sinus or the nasopharynx (Piquet 1950, Church & Uhler 1959, King, 1959, Mashberg *et al.* 1960) and may possibly have been developed from displaced cells of the ectodermal olfactory placodes during the embryonic stage.

A few cases of this tumor have been published as sympathicoblastomas on account of the similarity of microscopical features, and Escat (1931) considered the sphenopalatine ganglion as the origin, but if so, most esthesioneuromas should be localized in the nasopharynx. Besides, there is an important clinical difference between sympathicoblastoma and olfactory esthesioneuroma, as the former tumor is highly malignant and occurs almost exclusively in infancy and early childhood, whereas the latter is a relatively benign lesion of the adult. The urinary excretion of 3-methoxy-4-hydroxymandelic acid (VMA), which is the chief breakdown product of catecholamines, is often increased in cases of tumors of the symphathetic nervous tissue. In the present case the urinary excretion of VMA was found to lie within the normal range. The fact of VMA being normal could be taken as support for the view that the tumor is one of olfactory epithelial origin. The blood pressure was elevated, probably due to essential hypertension and not because of production of catecholamines in the tumor. Normal blood pressure is mentioned by some authors (Frühling & Wild, 1954, Mashberg *et al.* 1960).

Other suggested origins are the organ of Jacobson and the ganglion Loci of the terminal nerve, but these are not consistent with the usual localization of the olfactory esthesioneuromas.

Symptomatology

The olfactory esthesioneuroma occurs predominantly in adults with the greatest frequency in the age group ten to forty years. The youngest reported patient was a child, nine years old, and the oldest seventy nine. No great differential sex incidence has been established. The symptoms, which are non specific, begin with unilateral nasal obstruction, frequent epistaxis and nasal discharge, less often with excessive lacrimation or anosmia. When the tumor becomes locally invasive, there may be unilateral exophthalmos, diplopia, swelling of the root of the nose or headaches. Sinusitis, following blocking of the natural ostia, may cause the headache. The

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HYALINOSIS CUTIS ET MUCOSAE (LIPOID PROTEINOSIS)

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The features of lipoid proteinosis which are of particular interest to the laryngologist are reviewed. It is suggested that raised serum alkaline phosphatase of the case described could be the result of increased lipoglycoprotein synthesis and that one long term consequence of this is endocranial calcification. The latter has been clearly localised. It is also suggested that in a family in which lipoid proteinosis occurs in one member the raised serum alkaline phosphatase may perhaps be taken as an indication of latent lipoid proteinosis in an otherwise clinically normal member.

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The buccal mucosa, the palate and uvula, the faucial pillars, gums and the floor of the mouth can be similarly affected either by discrete plaques or by widespread infiltration, and the tonsils, in particular, are often prominent with thick yellow or white plaques of the affecting substance (Heyl, 1963; Jensen, 1962).

The movement of the tongue is considerably restricted, partly from its own general involvement but mainly because it is tethered to the floor of the mouth by the affected surrounding mucosa and in particular by the frenum which becomes a firm inelastic cord, often limiting the projection

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of the tongue to the dental margin The tongue itself is firmer than usual and can be almost woody hard (Caplan 1962 Dickey & Davis, 1964)

The anterior nares, like the lips, lose their normal softness and capacity to widen by the dilator nares and may become narrowed The nasal mucosa is less commonly affected, though there can be an associated atrophic rhinitis (Cowan *et al* 1961) However a similar mucosal change can extend from the post nasal space over the posterior pharyngeal wall to the laryngo-pharynx The thickening and reduced mobility of the pharyngeal wall associated with this may lead to some dysphagia and this sensation is occasionally made worse by a grossly thickened epiglottis (Lower 1948 Raymond Jones, 1965)

The aryepiglottic folds stand out as white, thickened uneven, glistening or granular bands and the process extends down on to the mucosa of the arytenoids, causing some limitation of movement of the crico-arytenoid joint Both the false and true vocal cords are similarly affected, the latter often having a rather nodular margin, thus increasing the huskiness of the voice (Caplan 1962 Cowan *et al* 1961 Dickey 1964 Scott & Findlay 1960)

However the process need not necessarily involve all the upper respiratory tract and while one part may be grossly involved, another may be clinically quite clear Though the prognosis on the whole is good in these cases, the most common danger to life is one of upper respiratory obstruction and of the 14 cases reported by Urbach & Wiethe, 1929 no less than 8 eventually required tracheostomy

Having pointed out those aspects of lipoid proteinosis which are of particular interest to the laryngologist the following case of a boy aged 18 years presents a varied pathology and is of general interest It is particularly interesting because of the precise localisation of the intracranial calcification present the long follow up of his laryngeal changes, and also the abnormal bio-chemistry of himself and of his sister who was otherwise clinically normal

Case Report

A schoolboy then 15 years old, was first seen at the Royal Infirmary Manchester in November 1962 He had spoken in a whisper from birth and had been husky ever since He had always had to drink lukewarm rather than hot fluids and could never put his tongue out even from an early age Some small warty outgrowths had developed on his knees at the age of 6 years and these had been removed by a local cautery They had recurred at the age of 11 years and at that time he also developed warty hyperkeratotic plaques on the elbows. The skin of the back of his hands and of his axillae was rather fixed and waxy and there was loss of the normal contours of both pinnae Small pearly bead like lesions had studded his eyelids from the age of 11 years (Fig 1)

There was no family history of skin disease or of hoarseness, nor was

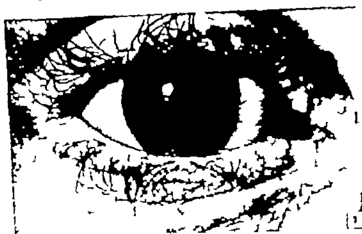


Fig. 1. Pearly bead-like lesions surrounding the eyelids.

there any consanguinity. Clinical examination of the father aged 40, the mother aged 44 and the sister aged 9, including their upper respiratory tract, was normal.

In August 1950, at the age of 2, a direct laryngoscopy had shown a small cyst of the posterior third of the left aryepiglottic fold and this was removed. A further direct laryngoscopy in October 1951 revealed another cyst in th same position. An attempt was made to remove this cyst but the material collapsed and no biopsy specimen could be obtained. He was kept under repeated observation and in May 1954 direct laryngoscopy showed a *general* thickening of all parts of the upper aperture of the larynx. No further cyst was present. A web was reported anterior to both aryten id areas in September 1955, nd in November 1956, direct laryngoscopy under light anaesthesia showed that the movements of both ocal cords were within normal limits. By December 1961 direct laryngoscopy re ealed a considerable thickening of the epiglottis and a d tailed view of the vocal cords was almost impossible to obtain. During 1962, there was a considerable thickening of the tissues of the tongue and a general tightening of the mucous membrane f the pharynx and lips.

In December 1962, at the age of 14 he was 122 lb. and slightly obese for his height of 5 ft. 2 in. By this time he had developed quite marked changes of the m uth and pharynx (Figs. 2 *a* and *b*). An absence of the upper lateral incisors can also be seen. The nasal mucosa and ears were quite normal.

With direct laryngoscopy the true and false vocal cords appeared to form one solid block of ti sue with a slightly irregular margin and without an int rvening entricle. Under light anaesthesia this cordal mass was seen to be sluggishly mobile. An upper oesophagoscopy and a proctoscopy at the same time showed *only normal mucosa.*



FIG. 2. Gross In ol ement f b rc l c lty rophary x nd post l phary g l w ll



Fig. 3. Tomograms of larynx showing loss of laryngeal ventricle with thickening of true and false vocal cords.

Radiological Examination

Tomograms of the larynx showed that there was thickening of the ary-epiglottic folds and boundaries of the pyriform fossae. It confirmed the laryngoscopic findings by showing the complete loss of a laryngeal ventricle due to thickening of both true and false vocal cords (Fig. 3). No abnormality was demonstrated in the sub-glottic region. An X-ray of the skull showed bilateral parasellar calcification and tomography confirmed the presence of two semilunar areas of calcification on either side of the pituitary fossa approximately 2.5 cm from the mid-line (Figs. 4 a and b). Air encephalograms carried out by Dr G. A. Steele showed that the calcified foci were seen to lie in the medial wall of the temporal horn anteriorly presumably in the hippocampus. The medial placed linear streaks appeared to lie in the cortex over the medial surface of the temporal lobe antero-inferiorly. The chest X-ray and the axial and paraxial skeletal X-rays were normal.

Histology

The histological findings show the characteristic picture of lipoid proteinosis with an increase in hyaline material in the dermis causing narrowing of the rete pegs of the epidermis, and the vessels are prominent due to



FIG. 2. Gross in olvement of bu cal a ity oropharyn d post l ph ry g al wall



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Fig. 4 a and b Lat ral vi w nd A P T mogram sh wi g bil ter l pa asell le flca ti n Th re are two l ifi d foci n ith side

a cuff of hyaline material around them (Fig 5) Similar histological pictures have been reported by Ungar & Katzenellenbogen and by Laymon & Hill in 1957 McCusker & Caplan in 1962 have thought that the hyaline deposit in lipoid proteinosis consisted of a glyco-protein with associated



FIG. 5. Biopsy from eyelid. (Haem t xyll and eosin.)

free or loosely bound lipid, and they suggested that the disorder should be more accurately labelled lipoglycoproteinosis.

Biochemical and Blood Studies

In December 1962, liver function tests including serum bilirubin, thymol turbidity S.G.O.T S.G.P.T plasma proteins and their electrophoretic pattern were all normal However at that time the serum alkaline phosphatase was levated at 35 units per 100 ml, though the serum calcium and serum inorganic phosphorus were normal. The glucose tolerance test and sensitive glucose tolerance test with Cortisone for latent diabetes were both negative, and the protein bound iodine and radio-acti e iodine uptake showed no thyroid deficiency Estimation of serum lipids, including serum free cholesterol, total fatty acids and neutral fat were within normal limits. The urinary calcium, inorganic phosphorus and the faecal fat were n rmal, though there was an occasional positive or weakly positi e faecal occult blood. The C.S.F and an electroencephalogram in December 1962 were normal, but in March 1963 an electroencephalogram reported that the delta activity was slightly more prominent and asymetrical on the right than the left Repeated e timations of the abo e tests of li er function showed no change from normality with the exception f the serum alkaline phosphatase lev l which remained at between 33 units and 38 units and in August 1963, increased to 52 units t the time when there was increased mobility of the tongue nd impro ement in the laryngeal picture.

Examination of the serum lipids of the father mother and sister were

all normal but though the serum alkaline phosphatase of the parents was normal the sister's was repeatedly about 35 units/100 ml The sister's liver function tests, serum calcium and phosphorus and X rays of the axial and paraxial skeleton were normal Further examination of the brother now aged 18 years, recently in August 1966 showed no change in the clinical picture but for a slight loosening of the buccal and pharyngeal mucosa Clinical examination of his sister aged 13 years, was normal. Biochemical tests of serum lipids, serum calcium and phosphorus were again normal in both, as were their liver function tests except for a raised serum alkaline phosphase of 22 units in the brother and 29 units in the sister both showing liver isoenzyme activity

DISCUSSION

Some 20 cases of lipoid proteinosis have been described to date with endocranial calcification Ramos e Silva in 1943 thought this occurred in the Dural Folds and since then it has been described in the temporal lobes, in the hippocampus and above the pituitary fossa (Caplan, 1962 Heyl, 1963 Dickey 1964) By carrying out air encephalograms and tomograms it has been possible to localise more precisely the position of the calcification In this case two areas of calcification can be clearly seen on either side of the mid line and it is possible that hitherto these have been interpreted as one

Many attempts have been made to explain endocranial calcification and particularly of the basal ganglia in association with parathyroid deficiency In the latter the clinical manifestations are the direct consequence of hypocalcaemia and hyperphosphataemia The solubility product of calcium and phosphate ions tends to be elevated and osteoclastic activity is reduced so there may be some increased calcifiction of bone, and certain soft tissues, particularly the basal ganglia may show metastatic calcification Milne in 1951 found a high concentration of phosphatase in the basal ganglia. In this case, repeated estimations of serum calcium and phosphorus were normal and the serum alkaline phosphatase was high Could this have been sufficient to be related to the endocranial calcification in both hippocampal regions?

Extensive investigations of the consistently raised serum alkaline phosphatase of the boy and also of his sister failed to show any other evidence of liver or bony disorder However since the alkaline phosphatase showed liver isoenzyme activity its raised level would seem to be indicative of an early involvement of the liver insufficient to show any abnormality in other liver function tests. Alternatively it has recently been shown by Warnock (1966) that there may be some functional similarity between endothelial phosphatase and that in the liver and the increased level may be related to the liberation of endothelial phosphatase in association with

the synthesis of lipoglycoprotein over a wide area of skin, mucous membrane and glandular tissue. It was noted in his case that there was an increase in serum *alkaline phosphatase* at the time when there was increased mobility of the tongue and larynx. It could be that the sister also has latent lipoid proteinosis, the steady raised level of serum alkaline phosphatase in *the sister who was without clinical changes, being explained* by there being an equilibrium between the anabolic and catabolic processes in the formation of lipoglycoprotein. Cases have been reported in which lipoid proteinosis developed in a hitherto normal adult. In Sulzberger's case (1942) the changes appeared after a severe sore throat. The condition is also known to be familial and in those reported by Jensen (1962) and by Scott & Findlay *(1960) it is seen that the clinical appearances* occurred later in some members of the family than in others. Thus, it may be that if the sister is a case of latent lipoid proteinosis, even a severe upper respiratory infection may upset the balance of equilibrium and that she may yet develop *clinical manifestations of lipoid proteinosis.*

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ZUSAMMENFASSUNG

Die Eigenart von *Lipoid-Proteinose, die* von besonder m Interesse für den Laryngologen sind, wurd n dargestellt. Es wird angenommen, dass die erhöhte alkalische Serum-Phosphatase des beschriebenen Falles wohl die Folge der erhöhten *Lipoglycoprot in-Synthese ist u d dass* nach langerer Zeit als weitere F lge endocraniale Kalzifikation auftreten kann. Die letztere ist hier zum erstenmal deutlich nachgewiese worden. Es wird ebenso angenommen, dass innerhalb *iner Famil der Lipo dprot inose* nur bei einem Mitgl ed uftritt, eine erhöhte alkalische Serum-Phosphatase bei einem sonst klinisch ollständig gesunden M tglied vielle cht als n Anzeichen einer latenten Lipoidproteinose *erstanden werden kann.*

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HISTOLOGICAL INVESTIGATIONS OF OTOSCLEROTIC FOCI

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A light microscopic study of 237 temporal bones revealed 27 cases of definite histological otosclerosis. The incidence localization activity and number of otosclerotic foci are reported. The present material differs from previous similar studies of temporal bones in showing the incidence to be highest in the age range 65–80 years and the activity in the otosclerotic foci to bear no relation to age. Furthermore the number of otosclerotic foci was largest in elderly persons.

Histological examination of temporal bones from patients with clinically manifest otosclerosis nearly always shows the otosclerotic foci to be localized around the oval window and to be accompanied by ankylosis of the stapes. According to several investigations, however histological otosclerosis in unselected materials is about 10 times as common as clinical otosclerosis (Engström, 1939 Guild, 1944 Nylén, 1949) In such investigations the frequency of stapedial ankylosis is lower as the majority of otosclerotic foci have not caused ankylosis of the stapes, even though they are localized to the anterior edge of the foramen ovale (Guild, 1944)

Otosclerosis is primarily a bone disease of the labyrinthine capsule, and the ankylosis of the stapes is an occasional complication which results in hearing impairment. We do not know why the lesion does not always encroach upon the annular ligament thus leading to stapedial ankylosis. Why the lesion only now and then affects the footplate of the stapes is an even greater mystery

The operative treatment of otosclerosis has afforded a possibility of obtaining active otosclerotic bony tissue for histological examination unlike the previous studies of post mortem material. This has introduced new views on the pathogenesis of otosclerosis. It has been found, among other things, that active otosclerotic foci show signs of healing rather than of dissemination of the disease (Simson Hall 1963) Comparison of the clinical signs of progressing hearing impairment and the histological findings has shown that it is not the active, progressing disease which causes the hearing impairment, but the process of healing.

Increased interest in otosclerotic foci has, by histochemical and electron microscopic studies in recent years (Chevance & Clerc, 1965 and Chevance, 1962) divulged further data concerning the histopathology of the disease.

Locally in histological foci abnormal quantities of mucopolysaccharides and increased amounts of alkaline phosphatase as well as sulph hydryl groups have been found By electron microscopy Chevance demonstrated accumulation of acid mucopolysaccharides and simultaneous disintegration of the collagen fibrils. On the basis of these changes of the labyrinthine capsule and studies of the connective tissue in skin biopsies some authors (Arslan & Ricci 1963 Stadil 1961 Bentzen 1967) have suggested that otosclerosis should be interpreted as a local manifestation of a generalized connective-tissue disease These new diagnostic methods have opened up new roads with interesting possibilities for elucidating the pathogenesis of otosclerosis.

In spite of the advanced technique within electron microscopy as well as histochemistry which have now been applied to the study of otosclerosis, classical light microscopy is still of interest all the more so as such studies on major materials of temporal bones have in fact been rather sparse so far (cf Nylén and Guild) We therefore felt that it might be of interest to report the findings in our material of temporal bones In this study we laid stress on assessing the site incidence, and activity of the otosclerotic foci

MATERIAL

The material comprises 237 temporal bones from 155 patients ranging in age from 1 month to 91 years. A certain selection of the temporal bones took place but not in respect to the occurrence of otosclerosis.

Table 1 lists the findings in those temporal bones in which we found otosclerosis.

HISTOLOGICAL TECHNIQUE

The temporal bones were fixed in 10% neutral formalin, decalcified in a buffer solution of formic acid and sodium formiate (Kristensen 1949) and embedded in celloidin The prepared blocks were cut, on a special microtome into sections of approx 18 μ All the preparations were cut in the horizontal plane from the superior semicircular canal to the level of the cochlear aqueduct Every 10th section was stained with haematoxylin eosin The remaining sections were stored All stained sections were then studied systematically for otosclerosis

RESULTS

When speaking of otosclerosis it is important to distinguish between a clinical and a histological diagnosis, as also emphasized by Nylén (1949) Histological otosclerosis is often silent, as the disease does not cause hearing impairment until it has led to ankylosis of the stapes None the less, there

may be otosclerotic changes, spread diffusely in the bony labyrinth, isolated at the round window or more centrally around the internal auditory canal. Such pathological changes cannot be revealed with certainty except by histology However recent advances within radiology (in particular the introduction of tomography using a polytome) have afforded a possibility of demonstrating otosclerosis extending into the retrofenestral area (Münd nich, 1961 Jensen *et al.*, 1966 Valvassori 1966)

Incidence of Histological Otosclerosis

Among the 82 patients for whom we have both temporal bones, we found bilateral otosclerosis in 8 (9.7%) and unilateral otosclerosis in 5 (6%) Among 73 patients for whom we have only one temporal bone otosclerosis was present in 6 (8%)

Thus, among the 237 temporal bones we found otosclerosis in 27 (11.4%) —from 19 patients. Of these patients 14 were males (13.0%) and 5 females (8.5%)

The present material hardly permits any definite conclusion concerning the incidence of otosclerosis in men and women As is well-known, clinical otosclerosis is about twice as common in wom n as in men. Engström and Nylén found histological otosclerosis to be about equally common in both sexes. We are unable to confirm their finding. On the contrary our material showed a male preponderance (Jørgensen & Kristensen, 1967)

Unlike Guild (1944) we did not find otosclerosis in children Our youngest case was a woman aged 28.

Localization of otosclerotic foci

The localization of the otosclerotic changes is shown in Table 1 In 26 (96%) of the 27 cases the process was localized around the oval window in most cases anterior to the oval window extending a varying distance to the posterior aspect above or below the window

In 5 cases (19%) the otosclerotic process around the o al window was accompanied by fixation of the stapes resulting in ankylosis, while in 16 (59%) of th 26 cases there were attendant otosclerotic changes of the stapes, *but without ankylosis.*

We ha e not found any cases with otosclerotic changes exclusively of the stapes or in the other ossicles.

In 11 cases (41%) the otosclerotic foci at the oval window were accom panied by a focus at the round window However these foci were confluent in only 3 cases (17%)

From these figures it *may be seen* that the regions around the oval and the round window are in ol ved in the majority of cases. This is in keeping with previous experience

We found the cochlear capsule to be involved in 7 cases (26%) and in 2

Table I *Histological findings in 27 otosclerotic temporal bones*

Case no.	No of temporal bones	Age	Sex	Side	Oval window	Stapes	Fixation	Round window	Cochlear capsule	Meatus acusticus int mus	Area outside the labyrinthine bone capsule	Activity of the otosclerotic focus	No of otosclerotic foci
1	2	28	F	r	+	+						++	2
				l	+	+						++	1
2	2	37	M	r									
				l	+	+		+				++	1
3	2	40	M	r	+							++	1
				l									
4	1	47	M	l							+	+	1
5	1	50	M	l	+	+		+				+++	1
6	2	55	M	r									
				l	+	+						+	1
7	1	58	F	l	+							++	1
8	2	61	M	r	+							+	1
				l									
9	2	63	M	r	+	+			+			++	1
				l	+	+						++	1
10	2	64	M	r	+							++	1
				l	+							++	1
11	1	65	M	l	+							+	1
12	2	60	M	r	+							+	1
				l	+						+	+	1
13	2	70	F	r	+	+		+				+++	2
				l	+	+		+				+++	3
14	1	70	F	r	+	+		+	+	+		+++	1
15	2	71	M	r	+	+	+	+	+			+++	2
				l	+	+	+	+	+			+++	1
16	2	75	M	r	+	+	+	+	+			+++	1
				l	+	+	+	+	+			+++	1
17	1	79	F	r	+	+	+	+	+	+		+++	2
18	2	87	M	r	+	+	+					++	1
				l									
19	2	91	M	r	+		+	+				+++	2
				l	+							++	1

cases (7%) the foci were at the floor of the internal acoustic meatus Accordingly other parts of the bony labyrinthine capsule are involved in a large number of cases.

In 2 instances we found otosclerotic foci outside the capsule of the bony labyrinth One was an isolated otosclerotic focus in the lateral semicircular

canal of a 47 year-old man whose condition had been diagnosed as Menière's disease The other patient was a 60-year-old man with a history of radical mastoidectomy in whom the vestibule was found to be overgrown with connective tissue which, in a large marginal zone, had ossified into tissue of the otosclerotic type. These changes had continued into the cochlea where the scala tympani, vestibule and cochlear duct were replaced by vascular bony tissue of a mosaic pattern in the lower two-thirds of the cochlea.

As a rule the localization of the bilateral foci was symmetrical in both temporal bones.

Unilateral otosclerosis was found in 5 out of 13 patients for whom we have both temporal bones. This gives a somewhat higher percental distribution than shown by previous studies (Nylén and Guild) as usually the incidence of unilateral otosclerosis is stated to be 15–30%

Pathological bony changes, the so-called "blue mantles" were found by us not only in otosclerotic temporal bones, but also in temporal bones without otosclerotic foci In that case we considered the finding negative.

Activity of the otosclerotic foci

As is well-known, otosclerosis may be present clinically as well as histologically in various stages of activity We have grouped the histological activity as + ++ and +++ according to whether the foci showed low medium, or high activity When several stages were represented in the same temporal bone the preparation was classified according to the highest activity present

We found almost the same number of cases showing foci with high activity (10 cases) and medium activity (11 cases) Only 6 cases were classified in the group of low activity The activity in bilateral foci was nearly always the same.

Table I shows, moreover that active otosclerotic foci were found in the temporal bones of elderly patients, at variance with the current opinion (Jørgensen & Kristensen, 1967)

Number of otosclerotic foci

In 21 temporal bones (78%) we found only *one focus*. This incidence of single foci is somewhat higher than that reported by others. In the remaining 6 temporal bones we found 2 foci in five and 3 foci in one We did not encounte more than 3 foci in any temporal bone.

It has previously been believed (Nylén, 1949) that advancing age, and possibly continued growth of a focus, will tend to the fusion of several foci, so that the number of foci decreased after the age of 50 This is not confirmed by ou material. On the contrary the number of foci appears to be largest in the elderly 5 of the 6 temporal bones with more than one focus being derived from patients o er 70 years of age.

DISCUSSION

In a study of temporal bones for otosclerosis we made several findings of interest. In the first place we found the highest incidence in the age range 60–80 years (17.7%) (Jørgensen & Kristensen 1967) while Guild (1944) found the highest incidence in the age group 30–50. Secondly we found that the activity in the otosclerotic foci did not decrease with advancing age. For instance, we found a highly active focus in a man aged 91. Thirdly we found the number of foci within each temporal bone to be largest in elderly patients.

It seems probable, then that active otosclerosis is just as common in elderly as in younger persons and that ankylosis of the stapes is possible, at least theoretically at any time of life.

It would be very interesting to investigate a material sufficiently large to permit statistical conclusions as to whether the number and activity of otosclerotic foci increases or decreases with advancing age. The latter view appears to prevail.

It is known that otosclerosis may give rise to vertigo, tinnitus, and perceptive hearing loss—even in the absence of stapedial ankylosis. Even conditions interpreted as Menière's disease have turned out to be otosclerosis (Paparella & Chasin 1966).

We feel therefore that our findings must stimulate to increasing the efforts at further investigation in cases presenting diagnostic difficulties, especially in elderly patients.

Today we have no clinical method for ascertaining the degree of activity in otosclerotic foci in the area of the foot plate. For instance, a positive Schwartze phenomenon merely indicates that a focus is active in the promontorial area, but not necessarily around the foramen ovale.

Without doubt a number of cases can be disclosed by tomography using the polytome but a more detailed investigation can be done only by exploratory tympanotomy. This is a procedure which, even in the elderly causes little discomfort and which will no doubt be used with increasing frequency in the future.

ZUSAMMENFASSUNG

Lichtmikroskopische Untersuchungen von 237 Schläfenbeinen ergaben 27 Fälle mit sicher histologischer Otosklerose. Die Inzidenz, Lokalisation, Aktivität und Anzahl von otosklerotischen Foki werden beschrieben. Unser Material unterscheidet sich von früheren ähnlichen Schläfenbeinuntersuchungen, indem wir die grösste Inzidenz in der Altersgruppe von 60 bis 80 Jahren gefunden haben, die Aktivität in der otosklerotischen Foki steht in keinem Verhältnis zum Alter. Ferner finden wir die grösste Anzahl der otosklerotischen Foki bei älteren Menschen.

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DISCRIMINATION IN ELECTRIC TASTE

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Taste discrimination is measured by using electric taste stimuli. The results obtained from six subjects at three intensity levels support the contention that the size of differential threshold grows as a power function of stimulus intensity the exponent being 0 4 For the Weber ratio an average value of 0 14 was obtained This value lies close to the 0 15 for salt as reported in the literature When calculated and interpolated from the results 17 successive jnds were obtained up to the stimulus intensity of 120 μA Beidler s function was approximately linear from the 4th jnd onward

Discrimination in any perceptual modality is one of the factors on which the amount of information input depends Experiments on discrimination in gustation have been under study for about one hundred years since in 1869 Keppler published his first observations on differential thresholds (also called just noticeable difference, jnd △ I) in taste He studied the validity of Weber s law in gustatory perception and came to the conclusion that his results did not support the law

Since his time a number of papers have been published investigating the same basic question Various opinions have been expressed as to the validity of Weber s law Lemberger (1908) found deviation from the law in the upper and lower ranges. Fodor & Happisch (1922) agreed that the law is valid in the middle range Saidullah (1927) obtained results which support the law in the case of salt one of the four basic taste qualities. Kopera s results (1931) support the law but his Weber ratios are different for different stimulus solutions even of the same quality Bujas (1937) obtained constant Weber ratios for salt sweet and sour whereas Schutz & Pilgrim (1957) stated that the law was valid for bitter and found only slight deviations for the other taste qualities.

Studying jnds for salt Beidler (1961) obtained a linear correlation between the ratio (C/R) and (C) (C) being the concentration of the solution and (R) being the cumulative number of jnds.

One of the latest studies on taste discrimination is that of Fischer *et al* (1965) They report that the jnds from Lemberger s data are linear in a log log plot between the 7th and the 38th jnd, the axes being concentration of solution and size of jnd. This exponential function was already theoreti

eally proposed by Pütter in 1918 In their own experiments they find a constant for the Weber ratio for sucrose and sodium saccharinate.

Furthermore Fischer *et al* (1965) found the number of successive jnds as big as 40 In calculating the information capacity of the gustatory system v Skramlik (1963) states that every taste quality possesses 20 successive jnds.

The sizes of the relative differential thresholds (Δ I/I) Weber ratios, in the various taste qualities are given by Pfaffmann (1959) on the basis of the studies up to that time. They are also reproduced by Hensel (1966) According to him the mean values for the different taste qualities are 0.20 for sweet, 0 15 for salt, 0.25 for bitter and 0.21 for sour Fischer *et al.* (1965) report the value of 0 41 for sucrose. Great interindividual variations occur as shown for instance by the experiments of Schutz & Pilgrim (1957)

All these studies on taste discrimination have been conducted by using chemical stimuli for the four taste qualities. In the past years, however electric stimulation of the tongue has become of great importance because it is especially applicable in clinical testing of taste acuity Electrogustometers have been constructed in various otological centers to deliver suitable electric pulses. Electric stimulation of taste has been known since the time of Sulzer (1754) Both a.c. and d.c. stimulation have been proved to be effective, and in fact v Békésy (1964) obtained all four taste qualities by appropriate a.c. stimulation of various intensities and frequencies. A simple clinical electrogustometer on the other hand employs mostly d.c. stimuli and no special attention is paid to the quality of taste sensation evoked. With normal d.c. stimuli usually a sour-salty sensation is reported, but additionally there may be also bitter components.

Studying discrimination in taste, Bujas (1937) used also electric stimulation On the basi of his results he came to the conclusion that the Weber ratio for electric taste is not constant, but grows with increasing stimulus intensity

METHODS

The purpose of the present study was to measure differential thresholds of the elect ic tast using a conventional clinical electrogustometer

The electrogustometer used was developed at the Helsinki University Otolaryngological Hospital for routine clinical taste testing. The circuit diagram of this device has been published elsewhere (Jauhiainen *et al* 1967) With this electrogust meter d.c. stimuli ranging from 30 to 90 µA were deli ered from th electrodes to the tip of the tongue of the subject.

The task of the subject was to assess whether a test stimulus of about 1 sec duration given 2 sec after a standard stimulus of the same duration was stronger or weaker than the standard Test stimuli on both sides of

the standard were delivered in random order with three presentations of each stimulus until a value was reached where two of the three were reported different stronger or weaker respectively Three stimulus ranges were used 30 50 and 90 μA

Six of the hospital staff served as volunteers, each in six sessions, one session lasting 10 to 15 minutes

RESULTS

With the above mentioned technique a descending and an ascending differential threshold was obtained for every stimulus intensity The arithmetic means of the differential thresholds (△ I) and their standard deviations (s D) are given in Table 1 Table 2 shows the Weber ratios (△ I/I) calculated from the thresholds.

TABLE 1 *Differential thresholds (△ I) for electric taste stimulation in microamperes*

Desc – Descending threshold; Asc. – Ascending threshold.

	Intensity level														
	30 μA					50 μA					90 μA				
ubject	Desc.	s.D	Asc.	s.D	Mean	Desc.	s.D	Asc.	s.D	Mean	Desc.	s.D	Asc.	s.D	Mean
h.	6.7	0.2	5 0	0.0	5 9	9 2	0.5	5.8	0.2	7.5	10.0	0 4	6.7	0.2	8.4
l.	5 8	0 2	5.8	0.2	5 8	9 1	0.4	5 0	0.0	7 1	15.9	0.5	5.0	0.0	10.5
u.	5.8	0 2	5.8	0.2	5.8	10.8	0 4	5.8	0.2	8.3	10.0	0.5	7.5	0.3	8 8
ı	5 0	0.0	5 0	0 0	5 0	5.0	0.0	5 8	0.2	5.4	9 1	0.4	5.8	0.2	7.3
u	5.8	0.2	6.7	0.4	6.3	7.5	0.4	5 8	0.2	6.7	10.0	0.6	5.0	0.0	7.5
L	5.8	0.2	5.0	0.0	5.4	6.7	0 2	5 0	0.0	5.9	6.7	0.2	5.8	0.2	6.3
Mean	5 8		5 6		5 7	8.1		5.5		6.8	12.8		6.0		8.1
s.D	0.58		0.78		0.50	2.28		0.46		1.34	3.32		1 08		1.60

TABLE 2 *The relative differential thresholds Weber ratio (△ I/I) for electric taste stimulation*

	Intensity level								
	30 μA			50 μA			90 μA		
Subject	Desc	Asc.	Mean	Desc.	Asc.	Mean	Desc	Asc	Mean
Ah.	0.22	0 17	0.20	0.18	0.12	0 15	0 11	0.07	0 09
Al.	0 19	0 19	0.19	0.18	0 10	0 14	0 17	0 06	0.12
Ja.	0.19	0 19	0.19	0.22	0 12	0.17	0 11	0 08	0.10
Ju.	0.17	0 17	0.17	0.10	0.12	0 11	0 10	0 06	0 08
Nu.	0.19	0.22	0.21	0 15	0 12	0 13	0 11	0.06	0 08
Pl.	0.19	0.17	0.18	0.13	0.10	0 12	0.07	0 06	0 07
Mean	0.19	0.19	0.19	0.16	0.11	0.14	0.12	0 07	0.09
s.D	0.018	0 022	0.016	0.046	0 012	0 024	0.036	0.010	0 020

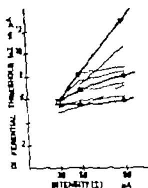


Fig. 1

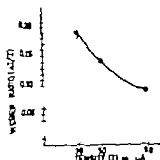


Fig. 2

Fig. 1 The means of differential thresholds for the electric taste plotted in linear coordinate system function of stimulus intensity. The circles (O) give the mean differential thresholds, the downward pointing triangels (▽) the descending differential thresholds, and the upward pointing triangels (Δ) the ascending ones. The weak lines give the mean differential thresholds for each subject.

Fig. 2. The Weber ratios plotted as function of stimulus intensity in linear coordinate system. The dots give the mean for each subject and the open circles the means of all the subjects.

When the results are plotted in a linear coordinate system, curves are obtained, which show that the Weber ratio is not constant, but a declining function with increasing stimulus intensity. Figures 1 and 2 provide the graphs in linear coordinate systems. Figure 3 gives the plot of differential thresholds as a function of stimulus intensity in a log-log-coordinate system whereby a straight line results. When the slope of this function is calculated the value of 0.4 is obtained.

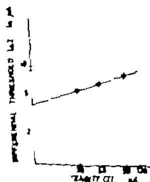


Fig. 3

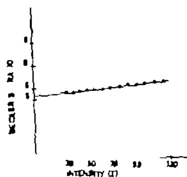


Fig. 4

Fig. 3. The means of differential thresholds plotted in log-log-coordinate system as a function of stimulus intensity. The dots give the means for each subject.

Fig. 4. The Weber ratio plotted as function of stimulus intensity up to 120 μA.

In order to get the Beidler's ratio the cumulative number of differential thresholds is calculated and interpolated from the results presented in *Fig.* 3. When the calculation is started from 10 μA, a value lying not far from the average threshold value (Krarup 1958) 17 successive thresholds are obtained up to the intensity of 120 μA. The Beidler's ratios (*C/R*) are plotted in respect to the intensity level (I) in a coordinate system in Fig. 4. A linear relation is obtained from the 3rd or 4th jnd upward.

DISCUSSION

The Weber ratio obtained by electric taste stimulation approximates the value 0.14. This result agrees rather well with the 0.15 given in the literature for chemical stimulation by salt. After all, electric stimulation of taste receptors evokes a sensation not far from salty.

When *the differential thresholds are plotted in a log log-coordinate* system, a straight line results. That corresponds with the idea that in electric taste stimulation the size of the just noticeable difference grows as a power function of the stimulus intensity.

The cumulative number of jnds, as calculated from our results, is 17. This is in a rather good agreement with the value of 20 given by v. Skramlik (1963). The upper limit of 120 μA has been taken in the present calculation *because the intensity function of electric taste* was *obtained* as a power function up to the intensity of 120 μA (Jauhiainen *et al.*, 1967). The change of the slope of this intensity function at that value possibly reflects the maximum of taste sensation, as discussed in the previous study.

The results also show the differences of descending and ascending threshold values. From this study it can clearly be seen that the difference to a decrease of stimulus intensity is more difficult to detect than to an increase.

In the previous study the authors obtained for the slope of the power function of electric taste the value of 1.2. This number and the exponent of the power function for jnds together characterize the information capacity of the gustatory system with electric stimulation.

ZUSAMMENFASSUNG

Das Unterscheidungsvermögen des Geschmacksinnes wird für elektrische Reizung der Zunge gemessen. Die an sechs Versuchspersonen bei drei Intensitätsstufen gewonnenen Ergebnisse stimmen mit der Vorstellung überein, dass der eben merkliche *Reizzuwachs* (Δ I) als *Potenzfunktion der Reizstärke* zunimmt (Exponent 0.4). Die Unterschiedsschwellen (Δ I/I) weisen einen Mittelwert von 0.14 auf, der nahe dem in der Literatur beschriebenen Wert für Salz (0.15) liegt. Aus den Ergebnissen werden bis zu einer Reizstärke von 120 μA 17 aufeinanderfolgende Unterschiedsschwellen berechnet. Die Beidler-Funktion ist von der 4. Unterschiedschwelle an näherungsweise linear.

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RETURN EYE MOVEMENTS, SACCADIC MOVEMENTS, AND THE QUICK PHASE OF NYSTAGMUS

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Electric stimulation of ampullary nerves in the alert cat and monkey induces active diphasic eye movements. These consist of an initial deviation followed by a movement which returns the eyes toward or past their initial position in the orbit. The second movement has been designated a return eye movement and is a central oculomotor reflex. This reflex appears to provide ocular compensation for head movements induced by strong impulses of angular acceleration Modulating influences on this reflex include vision head and eye movements, the initial position of the eyes in the orbit and the head on the neck, and the level of alertness. There is a reciprocal relationship between the amplitude of initial deviations and active return movements which varies linearly with changes in eye position Characteristics of return movements link them closely to saccadic movements and the quick phase of nystagmus, and differentiate them from other compensatory eye movements which have been previously described.

INTRODUCTION

We have previously shown that eye movements which follow ampullary nerve stimulation in the alert cat or monkey are bidirectional (Cohen *et al* 1967) The eyes initially deviate in a movement analogous to a tonic deviation or single slow phase of nystagmus This is followed by an active movement in the opposite direction which returns the eyes toward or past their initial position in the orbit This second movement termed a "return eye movement is a central oculomotor reflex It appears to coordinate compensatory head and eye movements during strong impulses of angular acceleration

This reflex is presumed to act in the following way When an impulse of angular acceleration or an ampullary nerve stimulus is weak, then an eye movement alone may provide satisfactory compensation When a stimulus is strong, however then compensatory movements of both the

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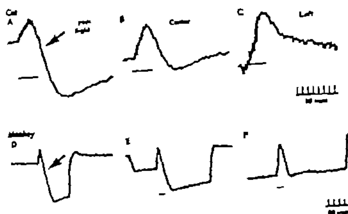


Fig. 1. Effects of eye position (initial deviation) and return eye movement in cat (*A–C*) and monkey (*D–F*). Animals were in light with head restrained. The EOG was recorded bitemporally with DC-coupling. The left lateral semicircular canal nerve was electrically stimulated for the period shown by the horizontal bar under each trace. An upward deflection of the trace in this and subsequent figures indicates an eye movement to the right. Return movement in *A* and *D* are marked by arrows. The time base for *A–C* is 10 msec per time marker shown under *C*, and for *D–F* is 50 msec per time marker shown under *F*. The initial deviation in C is about 15° and in *F* is about 20°.

head and eyes are induced. First the eyes move. Then as the head begins to move, the eyes flick rapidly in the opposite direction to counter the head movement. The rapid counter-deviation of the eyes is the return eye movement. Without it summation of a head and eye movement in the same direction would probably result in overcompensation of the gaze angle. Return movements are similar to the "anticompensatory eye movements" of Jones (1964). Thus the reflex is probably also present in humans.

In this report the analysis of return eye movements has been extended. Data is presented to show how the reflex is modulated and to demonstrate basic similarities which exist between return eye movements, saccadic movements, and the quick phase of nystagmus. From these data some properties of the neural organizations which initiate rapid eye movements have been inferred.

METHODS

Alert unanesthetized cats and monkeys (Macaca mulatta) were used. Eye and head movements were induced by stimulating semicircular canal nerves with 50 msec trains of 0.5 msec square waves at an intra-train frequency of 500/sec. Complete details of electrode implantation and methods of stimulation have been given in previous publications (Cohen, Suzuki & Bender 1964, 1965; Suzuki, Cohen & Bender 1964 *a*, *b*; Cohen, Tokumasu & Goto, 1966; Suzuki & Cohen, 1966). Although return eye movements are similar when any of the canal nerves are activated, for convenience only results of left lateral canal nerve stimulation will be

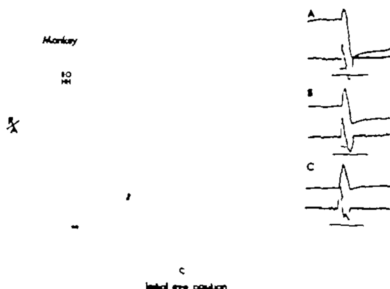


FIG. 2 Relati nship between amplitude of initial devlati n 4 return mo ements R and initial eye position A–C show eye movements induced from right, cent r and left initial eye positions, respectively The top trace of each pair i the DC-EOG The bott m trace i the differentiated EOG The room was illuminated for the period sh wn by the lower l nger h rizontal bar unde each pair of traces. The mpullary nerv stimulus is signalled by the upper short r horizontal ba (see Method for det il) The largest return mo em nt (in A) is about 45 In the graph on the left the ratio R/A is shown on the ordinate and eye positi n n the abscissa. The letters L and R represent about 20° of riginal eye deviati n to left and right

described Such stimulation induces an initial eye and head deviation to the right and a return eye movement to the left in both cat and monkey (Cohen *et al* 1967)

Eye movements were recorded by registering changes in the corneo-retinal potential (EOG) across both eyes either with RC-coupling with a 3 sec time constant or with DC-coupling In each of the succeeding figures an eye movement to the right is shown by an upward deflection of the trace The EOG was differentiated by an amplifier with a 0 002 sec time constant In Fig 9 the differentiated record was rectified and amplified, and the velocity of the return movements was displayed alone in the third channel Eye movement recordings were taken with animals in the *light* (EO) or dark (EC) and with the head free (HF) or restrained (HH) The EEG was monitored in some cases using conventional technique

In two experiments special conditions were used

(1) In Fig 2 initial deviations and return eye movements were *analyzed* after a monkey had moved its eyes to different positions of fixation For this analysis it was necessary to reduce the spontaneous saccadic shifts without decreasing alertness and to direct gaze in desired directions. This was accomplished by placing *the animal in a darkened room A dim light* was briefly exposed. When it attracted the monkey's attention it was extinguished and an oscilloscope trace was begun Sample traces of eye movements are shown in Fig 2 A–C. The sweep triggered a light which

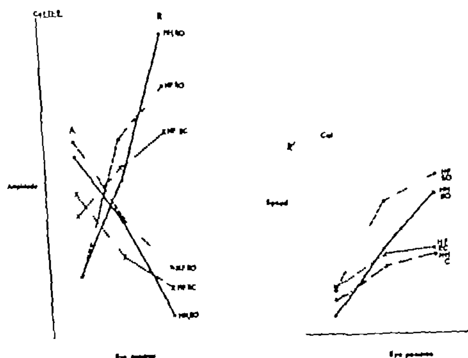


Fig. 2. Graphs showing the effect of eye position on amplitude of initial deviation *A* and return movement *R* (left) and on velocity of return movement *R'* (right). Data were taken from DC-EOG. Animals were in light (*EO*) or dark (*EC*) with their heads free (*HF*) or restrained (*HH*). *L* and *R* represent approximately 30° of initial deviation of the eyes to left and right in both graphs. Each point represents the mean of approximately 30 samples. The maximum difference between *A* and *R* under *HH EO* conditions is about 30°.

illuminated the room for the period indicated by the longer horizontal bar under each pair of traces. 100 msec after the onset of this light a 50 msec train of impulses was delivered to the left ampullary nerve (shorter horizontal bar). This proved to be effective in maintaining the monkey's attention. Both the initial deviation and return movement occurred in the light.

(2) In Fig. 3 return movements were induced during spontaneous nystagmus. This nystagmus followed a small vestibular nucleus lesion and was present only in the dark. This lesion did not disturb the pattern of canal nerve-induced eye movements.

RESULTS

As previously demonstrated return eye movements were largest in both cat and monkey when vision was present. In addition return movements were larger and faster in the cat when the head was free to move. Other factors which affected return eye movements included

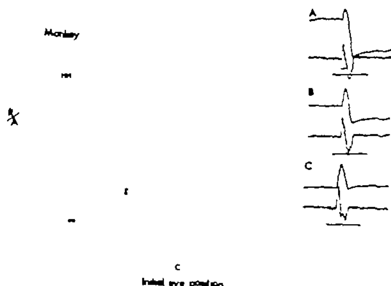


FIG. 2. Relationship between amplitude of initial deviations A return movements R and initial eye position. A–C show eye movements induced from right, centre and left initial eye positions, respectively The top trace of each pair is the DC–EOG The bottom trace is the differentiated EOG The room was illuminated for the period shown by the lower longer horizontal bar under each pair of traces. The ampullary nerve stimulus is signalled by the upper shorter horizontal bar (see Methods for details) The largest return movement (in A) is about 45 In the graph on the left the ratio R/A is shown on the ordinate and eye position on the abscissa. The letters L and R represent about 20 of original eye deviation to left and right.

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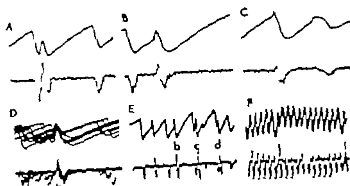


Fig. 5. Return eye movements during spontaneous nystagmus. Monkey in dark with head restrained. Upper trace is the RC-EOG. Lower trace is the differentiated EOG. Left lateral canal nerve stimulus is shown by the horizontal bar or dots underlying the lower trace of each pair (see Methods for details). In A–D stimulus artifacts are the time base (50 msec). Time base for E and F is 1 second, shown under F. Beats of nystagmus were approximately 10° ; amplitude A–C, initial deviations and return movements adapted to various times during the nystagmus cycle; D superimposed traces similar to A–C; E and F note slower time base. E, ampullary nerve stimulated at a–d; F ampullary nerve stimulated at 4 trains per second.

than grouping the absolute values of R or A. The ratio R/A tended to be linearly related to the position of the eyes in the orbit (Graph, Fig. 2).

The tendency toward a reciprocal relationship between initial deviations and return eye movements in different eye positions was present in both cat and monkey with the head free or restrained and with or without vision. This is demonstrated in Fig. 3. The graph on the left shows the effect of eye position on the amplitude of initial deviations (A) and return movements (R). On the right is graphed the effect of eye position on velocity of return movements (R). Consistent with previous findings (Cohen *et al.* 1967) the amplitude and velocity of return movements tended to be somewhat larger in the light than in the dark.

Eye movement

Effects of eye movement on initial deviations and return movements were different depending on whether the ongoing eye movement was slow or rapid in character. If rapid, either the initial deviation or return eye movement blended into the ongoing rapid eye movement if they were in the same direction or tended to be suppressed if they were in opposite directions. This is shown in Fig. 4 B and C during saccadic movements and in Fig. 5 E during the quick phase of nystagmus (in response to the "d" stimulus). In contrast when the ampullary nerve stimulus fell during a slow movement, as for example a slow phase of nystagmus (Fig. 5 A–C) then the reciprocal relationship between initial deviations and return eye movements dependent on initial eye position was similar to that found when the eyes were still. Soon after the end of a rapid movement, biphasic

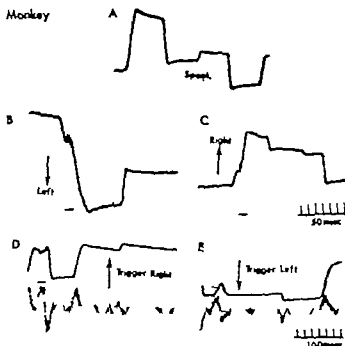


Fig 4 Return mov ment induced du ing saccadic mo ements and fixati n in light with h ad fixed Ampullary nerv pulse trains of 50 msec duration re shown by ho izontal bars in B–E A spontan ou saccadic shifts B and C ampullary nerve stimulati n during saccadic movem nts a ows (left and right) indicate direction of ng ing saccadic movem nt D an eye mov ment to the right nd E an ey m ement to the left were used to trigge the stimulu The lower trace in D and E i the differentiated EOG The time base f r A–C is 50 msec per time ma ker hown under C nd fo D and E is 100 msec per time m rke shown und r E The vertical rrows represe t ppro i mat ly 15 of ye m ment in B nd C and 30 in D nd E.

Eye position

The initial position of the eyes in the orbit affected both the amplitude and velocity of initial deviations and return eye movements (Fig 1) In both cat and monkey when the eyes were originally turned in the direction of the initial deviation i e to the right (A and D) then the initial deviation was small and the return eye movement was large The converse was true when the eyes were originally away from the direction of the initial deviation i e to the left (Fig 1 C and F) In this case the initial deviation was large and the return movement was small The latency of return movements was shorter when the eyes were in the direction of the initial deviation (Fig 1 A) than when they were away from it (Fig 1 B or C) The minimum latency of return movements was about 30 msec when the animals were in the light (Fig 1 A)

The relationship between eye position, initial deviations, and return movements was analyzed in the monkey Because successive eye movements from the same initial position varied somewhat in size, the ratio of the amplitude of the return movement induced by a single pulse train over the initial deviation from the same stimulus (R/A) was determined rather

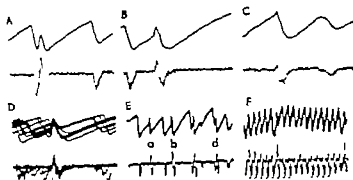


Fig. 4. Return eye movements during spontaneous nystagmus. Monkey in dark with head restrained. Upper trace is the RC–EOG. Lower trace is the differentiated EOG. Left lateral canal nerve stimulus is shown by the horizontal bar or dots underlying the lower trace of each pair (see Methods for details). In *A*–*D* stimulus artifacts are the time base (60 msec). Time base for *E* and *F* is 1 second, shown under *F*. Beats of nystagmus are approximately 20° in amplitude. *A*–*C*, initial deviations and return movements induced at various times during the nystagmus cycle. *D*, superimposed traces similar to *A*–*C*; *E* and *F* note slower time base. *E*, ampullary nerve stimulated at *a*–*d*. *F*, ampullary nerve stimulated at 4 trains per second.

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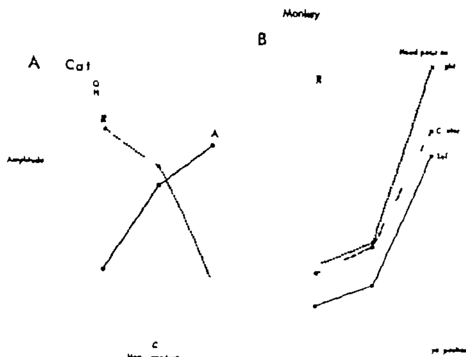


FIG. 6 Graphs showing the effect of head position on initial d viations and return ey mo ements. Each point represents the mean of 30 sampl s of DC-EOG s. Animals were in light with head centered or turned 45 to right or left. M vements in graph on left w e tak n with eyes in midposition. The maximum difference between A s or R's v 90° of head position change wa about 8 Effects of eye and he d position on eturn movements from different eye positions are shown in graph on right. L and R present initi l ey positions of 30° to left nd right. There is appro imat ly 30° of diff rence between the maxim m and minimum return m em nts.

eye movements dependent on initial eye position were again evoked by ampullary nerve stimulation (Fig 4 D and E)

It is apparent in Fig 4 D that return movements resembled saccadic movements when evoked from a stationary eye position On the other hand, return movements evoked during slow eye movements were identical in form and velocity to single quick phases of nystagmus (Fig 5 D and E) When return movements were induced more rapidly artificial nystagmus could be produced when the frequency of the pulse train repetition rate was about 4 per second (Fig 5 F) The initial deviations in this case were small but were present at the apex of each beat. They are shown by the upward deflection of the velocity trace at the onset of each stimulus. Four beats per second is close to the frequency of steady state nystagmus induced by ampullary nerve stimulation in the cat (Cohen Suzuki & Bender 1965) Cycling of artificial nystagmus may have been aided by suppression of succeeding quick phases after each return movement which lasted for several hundred milliseconds (Fig 5 D) Saccadic movements were also suppressed after return movements induced from a position of fixation This is particularly apparent in Fig 4 D but is present after each return

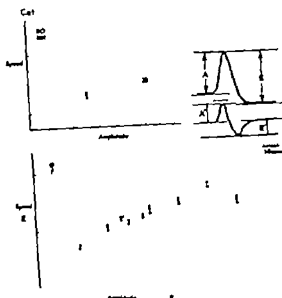


FIG. 7 Graph of relationship of amplitude and velocity of initial deviations (A and A') and return eye movement (B and B') in cat. Each dot represents one eye movement. Techniques for measuring amplitude and velocity are shown in insert on tracings of DC and differentiated EOG

movement (Fig. 1 D–F 4 E, and Fig. 8 of Cohen Goto & Tokumasu 1967)

Head position

Effects of head position on initial deviations and return eye movements was similar to effects of eye position. That is, initial deviations tended to be smaller and return eye movements larger when the head was turned in the direction of the initial head or eye movement (to the right) than when it was turned away from this direction (to the left). This is shown in the graph of Fig. 6 A. In both monkey and cat the effect of head position on return movements was considerably less than eye position but could be demonstrated whether the eyes were initially centered, to the right, or to the left (Fig. 6 B)

Relationship to other rapid eye movements

A number of similarities linked return eye movements, saccadic movements, and quick phases of nystagmus

(1) Return movements resembled saccadic movements when generated from a position of fixation (Fig. 4 D) and quick phases of nystagmus when induced during pursuit movements or slow phases of nystagmus (Fig. 5)

(2) There tended to be occlusive interaction between return movements and saccades or quick phases of nystagmus as well as suppression of other

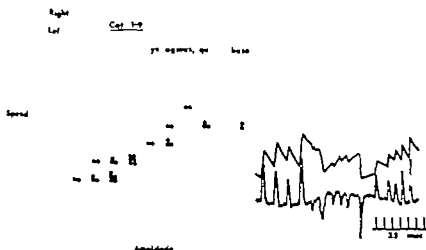


FIG. 8 Relationship between amplitud nd velocity of quick phases of nyst gmus in cat Nystagmus induced by pendular rotation in light first right, then left, and g in right. The RC-EOG (*top trace*) and differentiated EOG (*bott m trace*) re shown in the insert. Time base is 250 msec pe time mark r Largest beats of nystagmus were appro imately 30° in amplitude. Each dot in the graph represents on eye movement, closed circles being qui k phases to right nd open circle quick phases to left

rapid eye movements after return movements (Figs. 4 and 5) Return movements and slow movements did not interact similarly

(3) There tended to be a linear relationship between amplitude and peak velocity of return movements (Fig 7 lower graph) This also tends to be true for saccadic movements and quick phases of nystagmus in humans

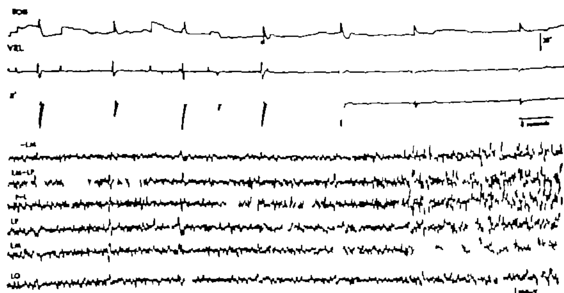


FIG. 9 Effects f alertnes on initial d lati n nd turn ye moveme t in m nkey Top trace is the DC-EOG sec d tra the differe tiated EOG, d third trace the diff rentiated EOG which was amplified and rectified to displ y locity f return movements in isolati n. *Below are ix derivati ns of the EEG Left lateral can l ner* stimuli given at point *a–g*



FIG. 10. Effects of alertness, drowsiness, and sleep on initial deviations and ret rn ey movements in monkey S perimposed tracings in light with head restrained. Horizontal line under C is 100 msec nd ertical arrow pproximat ly 20° of deviation to right.

(Dodge & Cline, 1901 Westheimer 1954 a Ueda & Suzuki, 1965) or in animals (Fig. 8) It is of interest, however that velocity characteristics of return movements were also found for initial deviations. Initial deviations are tonic movements closely related to the slow phase of nystagmus (Cohen *et al.*, 1964 Suzuki & Cohen, 1966) For example the velocity of initial deviations could equal or surpass that of return mo ements, quick phases of nystagmus (Fig 5) or saccades (Fig 9 a–c) In addition the maximum velocity of initial deviations also tended to be linearly related to the amplitude of the movement (Fig. 7 upper graph)

(4) *Active return movements* were present only in the alert animal and

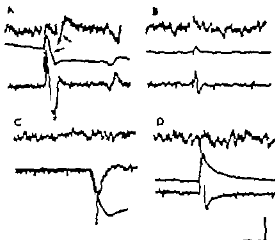


FIG. 11 Evoked pot ntials i lateral geniculat body f monkey which accompany rapid ey mov me ts in darkness. Top trace i each group is bipolar recording across the dorsal portion of the lateral geniculate body Second trace is the BC–EOG and third trace the differentiated EOG Time base show by the horizontal bar under D i 200 msec. Vertical ba represents 20° of ey deviation nd 100 microvolts. A stimulation f left lateral canal nerv l left monkey Return movement is followed by an evoked potential i the lateral geniculate body Both are show by arrows. A blink at the end of the trace is lso followed by imilar evoked potential. B, ampullary nerv stimulation in the drow y animal C nd D spont high locity movements of yes t l ft and right.

usually appeared in conjunction with a fast low voltage EEG (Fig 9 *a–e*) With the first appearance of drowsiness as manifested by a decrease in frequency and amplitude of saccadic movements, slight drooping of the upper lids, and a synchronized EEG both the amplitude and velocity of return movements decreased (Fig 9 *f* and *g* Fig 10 B) The time course and appearance of the ocular return in drowsiness suggested that it was probably largely passive Neither the amplitude nor velocity of initial deviations was much affected in initial stages of drowsiness (Fig. 9 *f* and *g* Fig 10 B) However as animals went into deeper sleep or under barbiturate anesthesia the amplitude and velocity of initial deviations was also decreased (Fig 10 C) Ampullary nerve stimuli at this time frequently induced eye deviations which lasted for hundreds of milliseconds. Saccadic movements and the quick phase of nystagmus are also differentially sensitive to decreased alertness. During drowsiness they may be markedly attenuated while slow movements or tonic deviations persist unchanged

(5) Each rapid movement of the eyes is associated with a potential in the lateral geniculate body in the dark (Feldman & Bender 1966 Cohen, 1965) A geniculate potential accompanying a blink is shown at the end of the top trace of Fig 11 A Similar potentials were also evoked by lateral canal nerve stimulation when return movements were induced (Fig 11 A, arrows) Lateral geniculate body potentials do not occur during pursuit movements or the slow phase of nystagmus. They were not induced by semicircular canal nerve stimulation in the drowsy state if a return eye movement was not induced (Fig 11 B) Lateral geniculate body potentials also do not occur during rapid passive deflections of the eyes (Fig 11 C and D)

DISCUSSION

Differences between pursuit and saccadic movements or the slow and fast phases of nystagmus have been apparent since the original studies of Dodge (1903) During pursuit movements and the slow phase of nystagmus vision is present, the angular velocity of the eyes approximates the velocity of the target (Henriksson 1955 Rashbass, 1961) and adjustments in angular velocity are continuous (Rashbass, 1961 Fender & Nye 1961 Stark, Vossius & Young, 1962 Robinson 1965) During saccadic movements or the quick phase of nystagmus on the other hand, vision and the pupillary light reflex are suppressed (Volkman 1962 Zuber Stark & Lorber 1966 Zuber & Stark, 1966) the velocity of the movement is related to the distance the eye has to travel (Dodge & Cline 1901 Ueda & Suzuki 1965) and the movements are beyond voluntary control once they have begun (Westheimer 1954 *b* Rashbass, 1961) Other differences include those of latency duration and sensitivity to barbiturates (Rashbass & Russell 1961 Robinson, 1965) On the basis of these differences Rashbass (1961) proposed that pursuit and saccadic eye movements are generated differently

Dodge originally described compensatory movements of the eyes which oppose head movements (1903) He noted that these compensatory eye movements had no measurable latency were characteristically smooth and slow and were uncontaminated by movements of the type exemplified by saccades (1921) From our data it is apparent that return eye movements are different from the smooth compensatory movements which he described. Instead they are similar to saccades or the quick phase of nystagmus. If Rashbass supposition is correct then all of these eye movements are probably generated by the same neural organization or mechanisms which are different from those which produce initial deviations, pursuit movements or the slow phase of nystagmus. Study of return movements may therefore lead to further insights into the way rapid eye movements are initiated or modulated. For example it has been shown in this study that velocity is not a true differentiating characteristic between initial deviations and return movements. This implies that tonic deviations or pursuit movements of equal rapidity could have been induced by natural stimuli which were capable of generating a highly coordinated input to the oculomotor system.

A number of factors have been shown to affect the triggering and am plitude of return eye movements. Perhaps most striking is the effect of ey position on initial deviations and return eye movements. This establishes a clear effect of eye position on succeeding eye movements. Changes in the amplitude of nystagmu due to changes in eye position are well known clinically but are usually considered to be a manifestation of Alexander s Law that is, due to the unequal elasticity of the eye muscles when the eyes are deviated toward or away from the direction of the slow phase (Carmichael et al 196.) However return eye movements are an active re flex phenomenon and any effect f eye position must have been neural in origin.

The question f how this eye position is sensed is of interest We have shown that neither passive deflection of the eyes (Fig. 11 C and D) nor VI nerve stimulation will initiate active return movements (Fig. 8 A of Cohen et al 1967) H nce it seems likely that eye position information which ultiated triggering f return mo ements was probably derived largely from intern l monitors of the xcitatory utfl w We would infer that feed back from muscle afferents was relatively unimportant in this respect Brindley & M rton (1960) ha previously demon trated that there is little consciou eye position sense

The data also show that the sense of head position summates with that f eye position in initiating return movements. These findings agree with previ u tudies which show that nystagmus may be produced by changes n the position of the head on the neck which do not stimulate the otolith organ (d Kleijn, 1921 Philipsson 1962) This emphasizes the important interaction which takes place between head and eye movements in the normal stat This interaction is usually disturbed in studies of pursuit or

usually appeared in conjunction with a fast, low voltage EEG (Fig 9 *a–e*) With the first appearance of drowsiness as manifested by a decrease in frequency and amplitude of saccadic movements, slight drooping of the upper lids, and a synchronized EEG both the amplitude and velocity of return movements decreased (Fig 9 *f* and *g* Fig 10 B) The time course and appearance of the ocular return in drowsiness suggested that it was probably largely passive Neither the amplitude nor velocity of initial deviations was much affected in initial stages of drowsiness (Fig. 9 *f* and *g* Fig 10 B) However as animals went into deeper *sleep or under* barbiturate anesthesia the amplitude and velocity of initial deviations was also decreased (Fig 10 C) Ampullary nerve stimuli at this time frequently induced eye deviations which lasted for hundreds of milliseconds. Saccadic movements and the quick phase of nystagmus are also differentially sensitive to decreased alertness During drowsiness they may be markedly attenuated while slow movements or tonic deviations persist unchanged.

(5) *Each rapid movement of the eyes is associated* with a potential in the lateral geniculate body in the dark (Feldman & Bender 1966 Cohen, 1965) A geniculate potential accompanying a blink is shown at the end of the top trace of Fig 11 A Similar potentials were also evoked by lateral canal nerve stimulation when return movements were induced (Fig 11 A, arrows) Lateral geniculate body potentials do not occur during pursuit movements or the slow phase of nystagmus. They were not induced by semicircular canal nerve stimulation in the drowsy state if a return eye movement was not induced (Fig 11 B) Lateral geniculate body potentials also do not occur during rapid passive deflections of the eyes (Fig 11 C and D)

DISCUSSION

Differences between pursuit and saccadic movements or the slow and fast phases of nystagmus have been apparent since the original studies of Dodge (1903) During pursuit movements and the slow phase of nystagmus vision is present the angular velocity of the eyes approximates the velocity of the target (Henriksson, 1955 Rashbass, 1961) and adjustments in angular velocity are continuous (Rashbass, 1961 Fender & Nye 1961 Stark, Vossius & Young, 1962 Robinson 1965) During saccadic movements or the quick phase of nystagmus on the other hand, vision and the pupillary light reflex are suppressed (Volkman 1962 Zuber Stark & Lorber 1966 Zuber & Stark, 1966) *the velocity of the movement is related* to the distance the eye has to travel (Dodge & Cline 1901 Ueda & Suzuki, 1965) and the movements are beyond voluntary control once they have begun (Westheimer 1954 *b* Rashbass, 1961) Other differences include those of latency duration and sensitivity to barbiturates (Rashbass & Russell, 1961 Robinson, 1965) On the basis of these differences Rashbass (1961) proposed that pursuit and saccadic eye movements are generated differently

Dodge originally described compensatory movements of the eyes which oppose head movements (1903) He noted that these compensatory eye movements had no measurable latency were characteristically smooth and slow and were uncontaminated by movements of the type exemplified by saccades (1921) From our data it is apparent that return eye movements are different from the smooth compensatory movements which he described Instead they are similar to saccades or the quick phase of nystagmus. If Rashbass supposition is correct then all of these eye movements are probably generated by the same neural organization or mechanisms which are different from those which produce initial deviations, pursuit movements or the slow phase of nystagmus. Study of return movements may therefore lead to further insights into the way rapid eye movements are initiated or modulated. For example it has been shown in this study that velocity is not a true differentiating characteristic between initial deviations and return movements. This implies that tonic deviations or pursuit movements of equal rapidity could have been induced by natural stimuli which were capable of generating a highly coordinated input to the oculomotor system.

A number of factors have been shown to affect the triggering and amplitude of return eye movements. Perhaps most striking is the effect of eye position on initial deviations and return eye movements. This establishes a clear effect of eye position on succeeding eye movements. Changes in the amplitude f nystagmus due to changes in eye position are well known clinically but are usually considered to be a manifestation of Alexander s Law that is, due to the unequal elasticity of the eye muscles when the eyes ar deviated toward or away from the direction of the slow phase (Carmichael *t al* 196‿) However return eye movements are an active reflex phenomenon and any effect of eye position must have been neural in origin.

The question of how this eye position is sensed is of interest. We have shown that neither passi e deflection of the eyes (Fig. 11 C and D) nor VI nerve stimulation will initiate active return movements (Fig 8 A of Cohen *et al* 1967) Hence it seems likely that eye position information which initiated triggering of return movements was probably derived largely from internal monitors of the excitatory outflow We would infer that feed back from muscl fferents w s relatively unimportant in this respect. Brindley & Mert n (1960) ha e pre iously demonstrated that there is little conscious eye position sense.

The data also show that the sense of head position summates with that f eye position in initiating return movements. These findings agree with previou tudies which show that nystagmus may be produced by changes in the position of the head on the neck which do not stimulate the otolith organs (de Kleijn, 1921 Philipszoon 1962) This emphasizes the important interaction which takes place between head and eye movements in the normal state. This interaction is usually disturbed in studies of pursuit or

saccadic movements by immobilizing the head Consequently there is little information on the effect of head movements on the saccadic system. Recently Atkin has shown that rather precise summation of head and eye movements occurs during natural gaze shifts (1964)

Very little is known about the trigger mechanism for either saccades or the quick phase of nystagmus, much less for return eye movements. However several characteristics of the trigger mechanism for return movements can be inferred from the data

(1) Return movements were recorded at shortest latency (30 msec) only when vision was present. At least 3–5 msec of this 30 msec latency must have been used to couple the eyes to the motor nerve activity (Cohen, Suzuki & Bender 1964) The remainder 25 msec or less, is then the true central latency of the reflex Since 25 msec is probably shorter than the minimum time it takes for information entering the retina to get to the calcarine cortex and back to the oculomotor nuclei of the brainstem (Cobb & Dawson 1960) visual pathways outside the geniculostriate system must have been responsible for early initiation of the response in the light. Pathways from the retina to the superior colliculus and pretectum are well known (Polyak, 1957) Since the latency from the retina to the superior colliculus is even longer than that of the geniculocalcarine system, it is likely that activity triggering return movements was carried in the other major retinal brainstem projection pathway i e the accessory optic tract system. Marg specifically noted in 1964 that units in the accessory optic tract could be activated with a latency of 20 msec. Recently Pasik have concluded that the accessory optic system is the critical structure for preservation of visual perception and optokinetic nystagmus in monkeys after bilateral occipital lobectomy (1966 and personal communication)

(2) The sensitivity of the system generating the quick phase of nystagmus to changes in the level of alertness is known from the studies of Collins (1962) Collins & Guedry (1962) and Crampton & Schwam (1961) The same is probably true for saccadic movements as well (Fig 9) Operationally we would agree with Collins (1962) that excluding barbiturates (Bergman *et al* 1952 Rashbass & Russell, 1961) or deep sleep (Dement, 1964) the frequency and velocity of rapid eye movements are among the most sensitive indices of the level of alertness of any including the EEG Here the finding that very rapid initial deviations can be induced during drowsiness although active return movements do not occur is of interest It shows that rapid eye movements themselves are not blocked by drowsiness. Instead probably the trigger mechanism for these movements is affected The same may also be true for saccadic movements and the quick phase of nystagmus

ACKNOWLEDGMENT

We should like to thank Mr Edward Murray for technical assistance

ZUSAMMENFASSUNG

Die elektrische Reizung der Ampullarnerven bewirkt bei sich im wachen Zustand befindenden Katzen und Affen entgegengesetzt Bewegungen Diese bestehen aus einer Bewegung, die das Auge auf den Originalpunkt oder daran orbeiführt. Die zweit Bewegung wird als „Return movement" bezeichnet und ist ein zentraler okulomotorischer Reflex. Dieser Reflex kann die Kopfbew gung verbessern, die durch Angularbeschleunigung desselben modaliert wird. Modulierende Einflüsse dieses Reflexes werden durch Sehvermögen, Bewegungen der Augen, des K pfes und Nackens und durch den Wachheitszustand des Tieres erkannt. Es besteht eine wechselseitige Beziehung zwischen der Amplitude der einleitende Abweichung und der Zurückkehr der Sicht, welche Variationen und Wechsel in der Position der Augen aufweisen. Die Charakt ristiken des „Return movement" sind mit Sakkadierung und Ruck Nystagmus verbunden und unterscheiden sich von anderen Augenbewegungen, welche früher beschrieben wurden

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EXPERIMENTAL STUDIES ON OPTOKINETIC NYSTAGMUS

II Normal Humans

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This st dy is an assessm nt of th f nctioning of the oculomoto neural refle in humans. Optoki etic stimuli ha e been applied by rotating large drum w th white tripes on the wall at different velocities around the subjects and the nystagmi movem nts were recorded lectronystagmographically In the first group f 18 subjects the responses va ied both i frequency and amplitud How er there seemed to be two general patterns. On pattern showed tendency toward small amplitude and high frequency nystagmu d th second pattern small frequency and large amplitud n stagmus. I the second group of 32 subjects two tests were made. During the first test the subject were in tructed to follow the stripes, d in the second t st re straight ah ad By follow ing the spec fic instructions, tw different sets of pt kinetic nystagmus responses were obtained that corresponded to the two patterns observed in the Group I periments. Whether stare or look" th responses f the ndi iduals sh wed a si ilarity to ach ther as indicated by the quant tat measurements of the different parameters of the nystagmus. Analys of th responses showed that th test ha e physi logical constan y and may be of exper m ntal and cl nical value

Previous experim nts in cats have demonstrated that an increase in the elocity f the ptokinetic timulus results in a change in the various parameters of the ptokineti nystagmu (i.e amplitude velocity of the slow component duration f the fa t and slow phases and frequency) The re lationship between the stimul nd the changes in the various parameters of th nystagmu wa significantly constant. By precise control of the stimulu it wa possible to make quantitati e estimates f the functional integrity of th ptokinetic reflex mechanism (Honrubia *et al.*, 1967) After these i itial observ tion in cats att ntion was directed to the study of the same problem in humans. As in the previous experiments, the optokinetic nystagmu was ev luated by electronystagmogr phic methods. Care w s taken to pro ide opt kinetic stimuli at v rious velocities and with small increment of magnitude This insured a more precise estimation of

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the relationship between the elicited optokinetic nystagmus and the strength of the stimulus than hitherto has been established (Ehlers, 1926 Gruttner 1939 Mackensen 1954 Enoksson 1956)

METHOD

A group of 51 subjects (19 males and 32 females) most of them students, was tested in this project To produce optokinetic nystagmus the subjects were seated in an adjustable chair at the center of a cylinder 50 inches in *diameter and 50 inches in height The bottom of the cylinder* was located 24 inches from the floor Head fixation was achieved by having the subjects resting their chins on a platform which placed their eyes in the center of the cylinder They were instructed not to turn their heads while the drum was rotating A black cloth formed the wall of the cylinder and 12 white stripes one degree wide were equally spaced vertically on the wall The velocity of the drum was controlled by a motor with an adjustable speed system The drum was surrounded by black curtains which provided isolation from the experimenter and recording apparatus Diffuse illumination *was provided through a white lucite top*

The variation of the corneo-retinal potential produced by the movement of the eyes during the nystagmic beat was picked up from two standard silver chloride skin electrodes placed on the outer canthus of each eye The ground reference electrode was attached to the subject s forehead By means of a Grass 7P1 d c preamplifier the potentials were differently recorded and displayed on the chart of the polygraph The magnitude of the change of the corneo-retinal potential produced by a given angular deflection of the eyes varies from subject to subject depending on among other factors, *the location of the electrodes with reference to the orbits* The mean value of the voltage recorded for one degree of deflection of the eyes was 16 μV Since the sensitivity of our preamplifiers and graphic recording systems is as good as 1 mm per μV the resolution of our recording system was sufficient for a detailed study of this problem Direct measurements were made from the actual recordings

RESULTS

The initial experiments were performed in 18 subjects who formed *Group* I Based on the information obtained from these experiments a second group of 32 subjects was tested which formed Group II The subjects in the second group were tested with two different methods and the results were described and classified under Subgroup A and Subgroup B

Group I *Optokinetic nystagmus obtained from subjects tested without receiving specific instructions*

This group was composed of 18 subjects Each subject was placed inside the optokinetic drum and advised that the drum was going to be

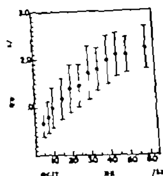


Fig. 1

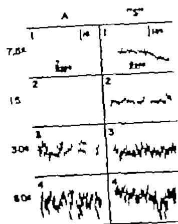


Fig. 2

Fig. 1 Graphical representation of the mean alues nd standard devi tions of the frequency measurement of optokinetic nystagmus elicited t different locities of the optokinetic drum.

Fig. 2 Photographs of recordings of the optokinetic ystagmus bt ined in tw subject A and "S" at different locities f the optokinetic drum.

rotated and they were asked simply to look at the stripes. In each instance the frequency of the elicited optokinetic nystagmus increased with the increase in velocity of the optokineti drum The frequency values obtained for any given v locity of stimulus showed large variations from subject to subject. This was evidenced by the standard deviations of the mean values of the frequency measurements (Fig. 1)

Th individual beha ior of this group of subjects varied, not only with reference to the frequency measurements, but also to the amplitude of the ny tagmus. Study of the records of the individual tests showed two distinct pattern f response One of the patterns was ny tagmus of low frequency and large amplitud The nystagmus of the second pattern was of higher frequency and small amplitud The nystagmus in each of the 18 subjects followed one or the other f the general patterns. The records of two individuals ha e been selected to demonstrate the two different types of re ponse (Fig. 2)

The frequency in all instances increased with increased velocity of ny stagmu but th amplitude behavior was distinctly different Individuals w th low freque cy curves (Subject A, Fig 2) showed nystagmus the am plitude of which diminished with increase in frequency The amplitude of the nystagmu of indi iduals with large frequency values (Subject S, Fig. 2 bec me larger a the frequency increased. Figure 3 shows graphically th nystagmu frequency produced at each velocity of the optokinetic stimulus in Subjects A and "S" Figur 4 demonstrates the amplitude measur ment for both ubjects. The values plotted in Figs. 1 3 and 4 re

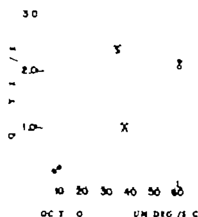


Fig. 3.

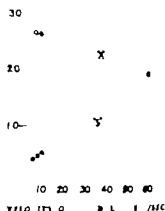


Fig. 4

Fig. 3 Graphical representation of the mean values of the frequency of the optokinetic nystagmus obtained in subjects "A" and "S"

Fig. 4 Graphical representation of the mean values of the amplitude of optokinetic nystagmus obtained in subjects "A" and "S"

the mean values of measurements of the nystagmus during a 30-second test interval

The records indicated that subject "A" kept his gaze fixed on the wall of the rotating cylinder during the slow phase of nystagmus for longer periods than subject "S" Consequently the nystagmus of subject "A" obtained larger amplitude than that of subject "S" Subject "S" in contradistinction performed more nystagmic movements per unit of time than subject "A" Although the behavior of the nystagmus for each subject was markedly different at lower velocities of the optokinetic stimulus, the difference was less apparent at higher stimulus velocities In this group of 18 persons 5 subjects were identified with behavior similar to subject "A" The records of the remaining 13 subjects were more like those of subject "S"

Group II *Optokinetic nystagmus in subjects after receiving specific instructions*

In a second group of 33 subjects the nystagmus was studied under two different conditions. In the first test they were advised to fix their gaze on a stripe and "follow" it with their eyes as far as possible without turning their head This was designated as the "look" test In the second test, the subjects were instructed not to follow the stripes but rather to keep their gaze straight ahead It was emphasized that they must "see" the stripes passing before them This was designated as the "stare" test

A *Optokinetic Nystagmus Produced by following the Stripes*

When the subjects were requested to follow the stripes the nystagmus was of large amplitude (Fig 5 left Fig 6 left) The subjects usually picked up a stripe and followed it for about 60° Some subjects became

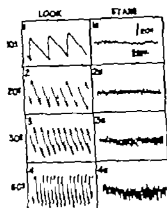


Fig. 5.

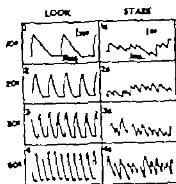


Fig. 6.

Fig. 5. Photographs of recordings of optokinetic nystagmus obtained in one subject of Group II in each of the tests, "look" (left) and "stare" (right)

Fig. 6. Photograph of recording of optokinetic nystagmus obtained in subject of Group II The nystagmus during the "stare" test was amplified both vertically and longitudinally (note calibration)

readily engaged in the optic reflex (Fig 5 left) in which each nystagmic beat was followed immediately by another In other subjects there was a pause between nystagmic beats (Fig. 6, left) The frequency of the nystagmus increased linearly with increasing velocity of stimulus (Fig. 7 "look")

During these tests the amplitude of the nystagmus remained relatively constant regardless of the velocity of the stimulus.

When the velocity of the stimulus was increased the nystagmic beat becomes double peaked at the end of the quick phase but still big deflections (Fig. 5, left Fig. 6, left) were produced. The mean values of the amplitude of the nystagmus shown in Fig 8, "look" are misleading since in the computation of the amplitude all the nystagmic beats both large and small were counted.

B Optokinetic Nystagmus Produced by following the Instructions to Stare Straight Forward at the Wall of the Drum

When the same subjects stared at the wall of the drum a *completely* different nystagmus response was obtained (Fig. 5, right Fig. 6 right) The eyes performed smaller amplitude movements at much faster rates than previously The frequency increased with increasing velocity of stimulus (Fig 7 "stare") The frequency almost doubled by increasing the velocity from 10 to 40 degrees per second. Further increases in the velocity of the stimulus did not bring a significant increase in the frequency of the nystagmus.

During this test the amplitude of the nystagmus became greater with the increase in the velocity of the stimulus (Fig. 8) The amplitude of the

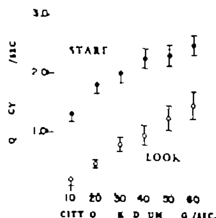


Fig 7

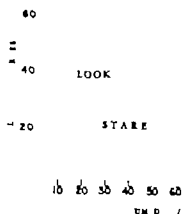


Fig 8

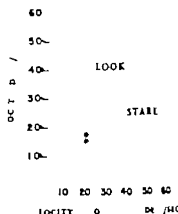


Fig 9

Fig 7 Graphic repre ntation of the mean values nd st ndard de iations f the fre qu ncy f the optokinetic nystagmus in both th st re and look tests at various v locities of the optokin tic drum The results were obtained from all subjects of Group II

Fig. 8 Graphic l representation of th mean alues of th amplitude f ystagmus obtained at various v lociti of the ptokin ti drum The results were obtai ed from th l st 14 ubjects tested

Fig 9 Graphical repre ntati n f the mean lue f the velocity of the l w component at lous lociti of th ptokin tic drum.

nystagmus during this test was smaller than that obtained in the previous test at all velocities

The computation of the velocity of the slow component of the nystagmus during the "stare test required the use of higher amplification of the signal than was used for the recording of the look" test In a group of 6 subjects the stare nystagmus was amplified both vertically and longitudinally to facilitate analysis of the velocity of the slow component (Fig 6, right) The mean value of the measurements made in these subjects at the different velocities of the optokinetic drum are graphically shown in Fig 9 The measurements demonstrated the ability of the subjects to follow the stripes closely at velocities as high as 60 per second during the look test During the "stare" test the velocity of the slow component showed an increasing lag as the speed of the optokinetic drum was increased

DISCUSSION

New information has been obtained which describes the difference between the nystagmus obtained under two different testing conditions The present work is a continuation and extension of observations made previously by other investigators (Ehlers, 1926 Gruttner 1930 Mackensen 1954 and Enoksson 1956) The use of specific instructions, electronystagmography and precisely contr lled optokinetic stimulation has enabled a more precise description of the relationships of the various parameters of nystagmus and the optokinetic stin ulus

It was possible to obtain two distinct patterns of nystagmic responses with physiologically constant characteristics. The nystagmic parameters (frequency amplitude and velocity of the slow component) are clearly dependent on the strength of the optokinetic stimulus.

Based on experimental work it has been postulated that there are two kinds of optokinetic nystagmus in humans (Ter Braak, 1936 Rademaker & Ter Braak 1948) These types of nystagmus were called the cortical or "look nystagmus and subcortical or "stare nystagmus. This classification was based on whether the cortex participated or was not involved in the nystagmic reflex. There is some evidence however that in man a functional cortex is necessary for the production of the optokinetic nystagmus (Velzeboer 1952 Roelofs, 1954)

The subjects in this experiment when under specific instructions to follow the stripes were performing a voluntary movement. If this voluntary motion is considered as nystagmus then this is a cortical nystagmus. Two *observations were made which provided some information* concerning the underlying mechanisms of the stare test After performing the "stare" test the subjects were surprised when informed of the frequency of their eye mo ements. In addition the velocity of the slow component during the stare test behaved similarly to the elocity of the slow component in cats (Honrubia *et al* 1967) These animals are believed to exhibit only the subcortical stare" type of nystagmus. Whatever the mechanism of produc tion of the two types of nystagmus (look or stare) may be it appears justified to consider them as two distinct entities.

Precise definition of the optokinetic responses in humans as cortical or subcortical may not be correct Instructions for obtaining the two different patterns were derived from the observation of the responses from the first group of subjects. These individuals were not subjected to any indication of what *was expected f om th m* and *their responses must therefore be* considered as pontaneous. In the second group of experiments the two pecific sets f in tructions were based upon the observed behavior in the first xperiment Und r each set of conditions, "look" or "stare" *a pattern* of responses with a phys logical constancy was obtained. The quantitative lat nship enables determination of deviations from the normal.

Optokinetic nystagmus has been used successfully as a diagnostic test (Barany 1921 Sten ers, 1925 Fox & Holmes, 1926 Cogan & Loeb, 1949 Carmich el, D x & Hallpik 1954 En kson, 1956 and Kestenbaum 1957) These test were not alwa performed using well standardized methods. Qu ntitat test similar to those *performed* during this investigation can pro ide new i formation concerning the opt kinetic neural reflex are in n rmal and pathol gical states

ZU SAMMENFASSUNG

D ese Forschu g st ein Einschatzung des Fu ktionieren des Augenmot r ers nreflle es in Me schen. Opt kinetische Reize wurden gewandt ind m man

eine grosse Trommel, an deren Wand sich weisse Streifen befanden, zu verschiedenen Geschwindigkeiten um das Subjekt drehte und die nystagmischen Bewegungen wurden elektronystagmographisch aufgezeichnet. In der ersten Gruppe von 18 Subjekten waren die Reizbeantwortungen verschieden in Häufigkeit und Amplitude Zwei allgemeine Muster schienen jedoch vorhanden zu sein. Eines der Muster zeigte eine Neigung für Nystagmus von geringer Amplitude und grosser Häufigkeit das andere Muster für Nystagmus von geringer Häufigkeit und grosser Amplitude. In der zweiten Gruppe von 32 Subjekten wurden zwei Proben unternommen In der ersten Probe wurden die Subjekte angewiesen den Streifen zu folgen und in der zweiten geradeaus zu starren In der Ausführung der spezifischen Anweisungen wurden zwei verschiedene Reizbeantwortungsgruppen des optokinetischen Nystagmus erhalten welche den in der Gruppe I Probe beobachteten zwei Mustern entsprachen Unter den Anweisungen „starren" wie auch „zusehen" zeigten die Individuen eine Ähnlichkeit zueinander wie es durch die quantitativen Messungen des verschiedenen Parameters des Nystagmus hervorgebracht wurde Die Analyse der Reizbeantwortungen zeigte dass die Proben physiologische Beständigkeit haben und von Forschungs- und klinischem Werte sind.

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LYSOSOMAL ENZYMES IN THE INNER EARS OF KANAMYCIN TREATED GUINEA PIGS

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The activity of acid phosphatase N-acetyl β-glucosaminidase and β-glucuronidase were localized histochemically in 36 guinea pigs injected daily with kanamycin sulfate (250 mg/kg body weight) for 1 to 6 weeks. All three lysosomal enzymes showed essentially the same distribution pattern. Before the well-known microscopic damage developed in the outer hair cells, there was a temporary slight increase in intensity and area of enzyme activity. Afterwards, the histochemical reaction became gradually weaker and finally was negative. The inner hair cells underwent the same changes, but later. Ultimately all hair cells were destroyed by this ascending process. Likewise in the spiral ganglion cells enzyme activities initially increased then markedly diminished. These changes started in the apical turn and descendingly involved also the lower turns. Enzyme activities in the spiral ganglion cells returned to normal after cessation of treatment. It appears that histochemical changes in the ganglion cells are independent of the damage to the organ of Corti and therefore not associated with the well-known secondary changes in the ganglion.

Since Umezawa isolated kanamycin in 1958, this antibiotic has been widely used. Its ototoxicity was discovered soon, and well documented studies pointed to the outer hair cells as the primary site of damage. Although of considerable clinical importance the mechanism by which these cells are affected has been unknown.

The distribution and possible significance of lysosomal enzymes in the normal inner ear has been studied before (Ishii & Balogh, 1966; Ishii *et al.* 1967). It is generally accepted that lysosomes are involved in cell injury and necrosis; therefore we assumed that a histochemical study of lysosomal enzyme activity in the inner ear may shed light on the mechanism of kanamycin ototoxicity. This paper reports the histochemical changes in the inner ear of kanamycin-treated guinea pigs.

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TABLE 1 *Kanamycin treatment*

No. of guinea pigs	Weeks of treatment	Total dose (mg/kg body weight)
4	1	1 750
4	2	3,500
10	3	5,250
4	4	7 000
4	5	8 750
4	6	10,500
9	Controls	—

TABLE 2 *Recovery after kanamycin treatment*

No of guinea pigs	Time after finishing 6-week-course (10,500 mg/kg body weight), weeks
1	1
1	2
2	3
2	4

MATERIAL AND METHODS

A total of 45 young adult guinea pigs (weighing 250 to 300 g) were used. All animals showed a good pinna reflex and had no middle ear infection Intraperitoneal injections of kanamycin sulfate[1] (250 mg/kg body weight) were given daily to 36 animals for 1 to 6 weeks (Table 1) Animals were also killed at various intervals after completion of a 6-week-course of treatment (Table 2) Nine untreated animals served as controls

All animals were decapitated under light ether anesthesia and the temporal bones were removed and dissected immediately The tissue blocks were fixed in an ice-cold 4% formol-calcium solution for 24 hours, then decalcified in a buffered EDTA solution for 7 days (Balogh 1965 Ishii & Balogh 1966) Decalcified tissue blocks were frozen on Dry Ice and sectioned at 12 μ in a cryostat at -20 C. Sections were mounted on clean coverslips, thawed and dried at room temperature for 30 minutes

The activities of acid phosphatase (Barka & Anderson 1962) β glucuronidase (Hayashi *et al* 1964) and N acetyl-β-glucosaminidase (Hayashi 1965) were localized by using the various naphthol AS-BI salts of the corresponding substrates. In all instances, hexazonium pararosanilin was employed as a coupler Nuclei were counterstained with methyl green The specificity of the reactions was checked by incubating sections in media from which the substrate was omitted

[1] Kantrex Injection, Bristol Laboratories, Syracuse New York.

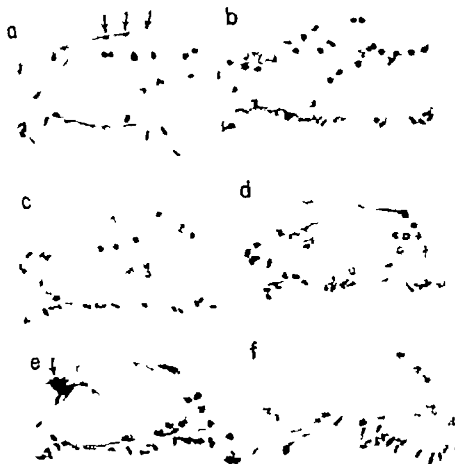


Fig. 1. Upper basal or 2nd turn of the organ of Corti of kanamycin-treated guinea pigs. The sites of N-acetyl-β-glucosaminidase activity are red but appear black on the micro-photographs. Cell nuclei counterstained with methyl green are round and are also dark on the photographs. Normal guinea pig. Enzyme activity was localized in the subcuticular area of outer hair cells (arrows) and in the inner hair cell. Enzyme activity throughout the supranuclear cytoplasm. (b) After 2 weeks of kanamycin treatment enzyme activity in the outer hair cells slightly increased in intensity and was localized ... the nucleus is closer to the top of ... hair cell (1st row). ( ) After 3 ... larger ... The ... becomes weaker and less sharply localized. (d) After ... treatment ... enzyme activity ... cells are missing and enzyme activity was no ... demonstrable ... enzyme activity is seen in the inner hair cell. (e) After 8 ... all outer hair cells are destroyed. In some instances the inner hair cells are still present and showed increased enzyme activity (arrow). (f) Same ... but the inner hair cell is lost.

In some instances, alternate sections were stained with oil red O for lipid or with ... stain. Some unstained sections were examined for autofluorescence with ... Zeiss fluorescence microscope using excitation filters Schott BG 12 (3 and 4 mm) and barrier filter No. 3.

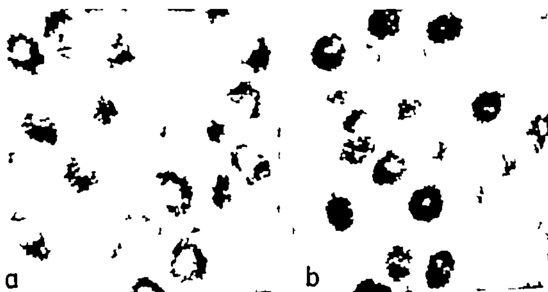


FIG 3 \ acetyl β-glucosaminid se tivity in the spiral ganglion cell of th basal turn in a normal gui a pig (*a*) and after 6 weeks treatm nt with kanamy in (*b*) \ sig nificant differences re recognized 610

enzyme activity was seen in any section through Rosenthal s canal Large azo dye granules were noted in a few normal ganglion cells. One to three weeks after kanamycin treatment there appeared to be more ganglion cells with large granules (Fig 2 *b*) These granules had no autofluorescence and failed to stain with Nissl s stain or with oil red 0 The majority of the ganglion cells however showed diminution of enzyme activity The loss of demonstrable enzyme activity was more striking in the upper turns After 4 weeks treatment the histochemical reaction was very weak in most ganglion cells (Fig 2 *d*) and by the end of the 6th week enzyme activity was demonstrable only in a few cells (Fig 2 *e*) At the same time the ganglion cells of the basal turns frequently appeared normal (Fig 3 *a* and *b*) After a full course of treatment, recovery began in 2 weeks and 4 weeks after cessation of treatment enzyme activities returned to normal in all ganglion cells (Fig 2 *f*)

No significant changes in enzyme activities were recognized in other parts of the cochlea or in the vestibular labyrinth

DISCUSSION

In agreement with numerous animal experiments we found that initially kanamycin affects the organ of Corti at the basal turn and later ascendingly damages the hair cells in the upper turns. In the earliest phase of kanamycin toxicity we noticed slightly increased amounts of azo dye deposits in the subcuticular area of outer hair cells. This observation correlates with recent electron microscopic findings in the early phase of kanamycin

otot xicity Lundquist & Wersall (1966) found the subcuticular lysosomes of the outer hair cells aggregated to form large dense bodies. Probably these alterations account for the slight initial increase in enzyme activity an teceding the well known degenerative processes in the organ of Corti Secondary changes have been observed in the ganglion cell population (Hawkins, 1959 Mesolella & Costa, 1960 Catalano *et al.*, 1961 Friedmann & Bird, 1961 Ward & Fernández, 1961 Beck & Krahl 1962 Reddy & Igarashi 1962 Ardouin *et al* 1963 Farkashidy *et al* 1963 Degreef 1964 Hawkins & Engström, 1964 Kohonen, 1965 Tanaka 1966) These changes are accompanied by depressed cochlear microphonics and action potential (Hawkins, 1959 Owada, 1962 Tyberghein 1962 Farkashidy *et al.*, 1963 Degreef, 1964) Human inner ears also show damage to the hair cells and loss of spiral ganglion cells in the basal turn after prolonged kanamycin therapy (Benitez *et al* 1962 Jørgensen & Schmidt, 1962)

In view of this ascending pattern of damage it was paradoxical that lysosomal enzyme activity in the ganglion cells demonstrated damage of a descending nature. Tho earliest recognizable change in the spiral ganglion was the appearance of large azo dye granules in the cytoplasm of some cells. These granules began to appear 2 weeks after kanamycin treatment and were most numerous after 3 to 4 weeks. Later stages were characterized by a marked diminution f azo dye deposits in all spiral ganglion cells, although the quality of the emaining dye granules did not change. These histochemical changes in the ganglion cells were reversible after cessation of treatment enzyme ctivity returned to normal Recent electron microscopic observ tion support our contention that the changes in the ganglion cells of kanamycin treated animals are partly primary and are not due to damage to the organ of Corti Awataguchi *t al* (1967) reported abnormalities in variou subcellular tructures, including the distension and in crease of Golgi vesicles. Since these organ lles are known to be rich in acid hydrolases (DeDu e 1963) abnormalities in their enzyme activities are not un xpected Sim ilar enzyme histochemical changes have also been produced xperiment lly in other ganglion cells. For instance transection of motor neuron n e uses triking increase of lysosomal enzyme activities in v rious pecies (Bu ke *et al* 1949 Cerf & Chacko, 1958 Colmant 1959 Barron & Tuneboy 1962 nd 1964 Söderholm, 1965 Blank & Oehlschlägel 1965 and 1966) In all these experiments, lysosomal enzyme acti ities t rted to incre se 3 days after nerve transection and remained levated about 4 week postoperatively Afterw rds, enzyme acti ities returned to n mal Ch nges closely resembling our findings were reported by Fisher & Sutherland (1965) who studied th nodose ganglion after transection of the cervical gu nerve and noticed increased acid phosphatase acti ity already 2 days postoperatively Similar to our results, they found th t fter the initial rise enzyme activity decreased and by the 25th day it wa ma kedly diminished. Thus, it may be assumed that kanamycin similarly d m ges the a on and causes non pecific changes in the piral

ganglion cells. Our findings suggest that the histochemical changes in the spiral ganglion are causally unrelated to hair cell damage because they are reversible and of a descending type On the other hand the changes in the hair cells and the secondary changes in the spiral ganglion cells are irreversible and of an ascending nature

Kanamycin and several related antibiotics are not only ototoxic, but also nephrotoxic While morphological changes in kidneys after kanamycin treatment have not been studied viomycin a similar polypeptide of low molecular weight damages renal lysosomes. After viomycin administration the renal tubular epithelium of rats degenerates and later becomes necrotic (Staemmler & Karhoff 1956) The early phase of this process is characterized by marked swelling of lysosomes, followed by their disintegration (Caesar 1965 Klein *et al* 1965) Concomitantly acid phosphatase activity first increased then diminished in the tubular epithelium (Gössner 1963) Thus the sequence of events in the kidneys appears analogous to that in the spiral ganglion cells after kanamycin treatment From these observations one cannot draw conclusions on the pathogenic mechanism of kanamycin toxicity but apparently both renal and cochlear damage involves the lysosomes

ZUSAMMENFASSUNG

Die Aktivität der sauren Phosphatase N Acetyl β-Glukosaminidase und ρ-Glukuronidase wurde histochemisch in 30 Meerschweinchen die während 1 bis 6 Wochen täglich mit Kanamycinsulphat (250 mg kg Körpergewicht) behandelt worden waren lokalisiert Die drei lysosomalen Enzyme zeigten im wesentlichen dasselbe Verteilungsmuster Bevor sich der allgemein bekannte Schaden in den äusseren Haarzellen entwickelte erhöhte sich die Intensität der Enzymaktivität vorübergehend etwas. Danach wurde die histochemische Reaktion allmählich schwächer und war schliesslich negativ In den inneren Haarzellen waren dieselben Veränderungen erst bedeutend später zu beobachten bis alle Haarzellen durch diesen ansteigenden Prozess zerstört waren In den Zellen der Ganglion spirale nahm die Enzymaktivität ebenfalls anfänglich zu, wurde jedoch bald auffallend schwächer und war nach 4 bis 5 Wochen kaum mehr nachweisbar Dieser Verlauf begann in der apikalen Windung und befiel absteigend auch die unteren Ganglionzellen Nach Unterbrechung der Kanamycin Behandlung kehrte in den Ganglionzellen das normale Verteilungsmuster der Enzyme zurück. Die histochemischen Veränderungen in den Ganglionzellen zeigten eine absteigende Tendenz scheinen deshalb von denen des Cortischen Organs unabhängig zu sein und sind nicht eine Folge der allgemein bekannten sekundären Degeneration

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OXIDATIVE ENZYMES IN THE COCHLEA

An Electron Microscopic and Histochemical Study of Succinic Dehydrogenase and Dihydronicotinamide Adenine Dinucleotide Diaphorase

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Recently developed formazan techniques for the electron microscopic localization of SDH and NADH-D revealed details about the way that these enzymes are distributed in the cochlea. The degree of activity that was manifested on light microscopy by each kind of cell correlated with its mitochondrial content. The stria vascularis was very reactive. Supporting cells showed more activity than hair cells. This technique revealed precise localization of activity on the membranes of mitochondria. NADH-D appears to be present in the parallel membrane and cistern system that is arranged longitudinally in hair cells.

Convenient histochemical procedures are now available for study of two interesting oxidative enzymes. Succinic dehydrogenase (SDH) and dihydronicotinamide adenine dinucleotide diaphorase (NADH D) formerly known as dihydrodiphosphopyridine nucleotide diaphorase, are two important enzymes in the oxidative pathway of Kreb's tricarboxylic acid cycle. Earlier work (Barrnett 1958, Sedar & Rosa, 1961, Nakai, 1965) involved localization of enzyme sites with the use of tetrazolium salts which became reduced to colored formazan. Recent reports have demonstrated the advantages of using 2,2'-3,3'-tetra-p-nitrophenyl-3,3'-(3,3'-dimethoxy-4,4'-biphenylene)-ditetrazolium chloride (TNBT) as a reagent for localization at the electron microscopic level of SDH and NADH D (Sedar et al. 1962, Rosa & Tsou, 1963, Sedar & Burde 1965, Ogawa & Barrnett, 1965). These enzymes cause deposition of a colored formazan of TNBT (tetra-p-nitrophenyl formazan, TNF). This formazan is desirable for electron microscopy because it is relatively insoluble in the customary reagents used for dehydration and imbedding, it resists the electron beam, and it forms very small particles (Sedar et al. 1962).

The formazan is a blue granular material that results when hydrogen

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OXIDATIVE ENZYMES IN THE COCHLEA

An Electron Microscopic and Histochemical Study of Succinic Dehydrogenase and Dihydronicotinamide Adenine Dinucleotide Diaphorase

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Recently developed formazan techniques for the lectron microscopic localization of SDH and NADH D re ealed details about the way that these nzymes are distributed in the cochlea. The degree of acti ity that was manifested on light microscopy by each kind of cell correlated with its mitochondrial content. Th stria ascularis was very reactive. Supporting cells sh wed more acti ity than hair cells. This technique revealed precise localizatio f activity on the membranes f mitochondria. NADH-D ppears to be present in the parallel m mbran and c stern ystem that is arranged longit dinally in hai cells.

Convenient histochemical procedures are now available for study of two interesting oxidative nzymes. Succinic dehydrogenase (SDH) and di hydronicotinamide adenine dinucleotide diaphorase (NADH D) formerly known as dihydrodiphosphopyridine nucleotide diaphorase are two im portant enzymes in the oxidative pathway of Kreb s tricarboxylic acid cycle. Earlier work (Barrnett 1958 Sedar & Rosa, 1961 Nakai, 1965) involved localization of enzym sites with the use of tetrazolium salts which became reduced to colored f rmazan Recent reports have demonstrated the advantages f using 2,2 3,3 tetra-*p*-nitrophenyl-3,3 (3,3 -dimethoxy-4 4 bi phenyl ne)-ditetrazolium chloride (TNBT) a a reagent for localization at the electr n microscopic le l of SDH and NADH D (Sedar *et al* 1962 Rosa & Tsou, 1963 Sedar & Burde 1965 Ogawa & Barrnett, 1965) These enzymes cause deposition of a col red formazan of TNBT tetra *p*-nitrophenyl formazan (TNF) This formazan is desirable for electron microscopy because it i relatively insoluble in the customary reagents used for dehydration and imbedding, it resists the lectron beam, and it forms very small particles (Sedar *et al* 1962)

Th formazan is a blue granular m terial that results when hydrogen

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FIG. 1. Org n of Corti Incubation fo SDH activity Hensen s and Deiters cells, nd the *region surrounding in er hair cells* show m re intense activity than the hair cells. Even the hair cells were faintly stained blu when xamined with the microscope (Light micrograph 300)

FIG. 2. Stria v scularis Incubation for SDH ti ity All layers f the tria showed intense staining (Light mi rograph 300)

atoms are transferred from supplied substrate to colorless TNBT When *sodium succinate* is provided the deposit is related to SDH activity If dihydrodiphosphopyridine nucleotide is supplied the precipitate indicates the localization of NADH D

We, like previous investigators have become interested in studying oxidative enzymes in the cochlea because the hair cells have a unique nutritive system They are not closely related to any vascular structures The reason for this isolation probably is to reduce acoustic noise that could otherwise interfere with the hair cells The hair cells are nourished via surrounding cells or fluid

The cochlear microphonic is the electrical result of hair cells activity and a substantial portion of it is resistant to oxygen deprivation (Misrahy *et al* 1958) Anerobic metabolism plays a role of unknown importance to hair cells

MATERIALS AND METHODS

Eighteen guinea pigs, weighing approximately 350 g each were used as the experimental animals.



FIG. 3. Mitochondria of the stria vascularis. Incubated for SDH. Dark or marginal cell mitochondria show more reactivity than the intermediate or light cells. The surface of mitochondrial cristae are the reaction site. (Electron micrograph × 100,000.)

The inner ear structures of anaesthetized guinea pigs were removed and immediately placed in an appropriate reagent. Much of the bone surrounding the cochlea was dissected away and some of Reissner's membrane, stria vascularis and spiral ligament was torn exposing the whole inner ear structure to the chemicals.

In the preparation of tissue the following procedures were employed

Substrate solution and control

1. Succinic dehydrogenase (SDH) medium: 5 mg of TNBT (1 mg/ml), 80 mg of sodium succinate in 10 ml of 0.1 *M* phosphate buffer (pH 7.6) and 0.44 *M* sucrose.

2. Dihydronicotinamide adenine dinucleotide diaphorase (NADH D) medium: 0.3 ml of 2.0 mg% TNBT, 0.3 ml of 1% NADH, 1.0 ml of 0.1 *M* phosphate buffer pH 7.8, 1.4 ml of distilled water, 0.23 g of sucrose.

3. Control media: The following control media were used with the above incubation.

(a) Substrate free medium.

(b) 700 mg sodium malonate was added to the incubation medium.



FIG 4 Out r hair cell incubated fo NADH D At some ites al g the parall l membra es lini g hair cells this nzym wa present (ar ows) (Electron micrograph 30,000)

FIG. 5 Higher m gnificati n h wing th fi e granular d po it which resulted from NADH D taini g in the hai cell i t rn (Electron micrograph 100,000)

FIG. 6 NADH D acti ity i l ai cell mitoch ndria nder high m gnificati n. Th deposit n of fo mazan n th mitochond i l m mbrane is well sh wn (Electro micrograph: 95,000)

PROCEDURES

1 The specimens were fixed in cold 6.25% hydroxyadipaldehyde or 4% formaldehyde with 8% sucrose in 0 1 *M* cacodylate buffer pH 7 6 for 30 minutes. After this prefixation the tissue was washed in several changes of 0 1 *M* cold cacodylate buffer pH 7 6 containing 8% sucrose for 2 hours. Then the material was incubated in the mixture designed for the demonstrating f r SDH and NADH D activity for 20–30 minutes at room temperature

2 Without any prefixati n the specimen was washed in cold 8% sucrose in 0 1 *M* phosphate buffer pH 7 6 for 15 minutes and incubated in the mixture described above for 20–30 n inutes at room temperature



FIG. 7 Distribution of mitochondria I orga of Corti Deiter cell ha rel th ly large number f mitochondria (*M*) (Electro microg ph 8,00)

FIG. 8. Mitochondria of the stri ascularis. Of the three kinds of ti ue of the cochlea, the stria has the highest co t nt of m tochond ia. (Electron micrograph 8300)

After incubation, the specimen was washed in cold 8% sucrose briefly and was then fixed in 1% cold osmium tetroxi le dehydrated through graded alcohols and propylene oxide and embedded in Epon plastic Thin sections were made by an LKB Ultrotome nd mounted on formvar-coated copper grids. All sections were ex mined without any additional staining in an RCA EMU 3G lectron microscope A Zeiss photomicroscope was used for study of free-hand sections.

Some specimens h ve been incubated in control media for 30 minutes in every experiment to rule out nonspecific reaction

RESULTS

The staining of each type of cell could be correlated with its mitochondrial content The more mitochondria a cell had, the more intense the staining as seen with light microscopy This would be expected, since most activity appeared on the cristae of mitochondria when examined with the lectron microscope.



F g 4 Out hair cell incubated for NADH D At som ites al ng the parall l membranes lining hair cells this enzyme was present (*arrows*) (Electron micrograph: 30,000.)

Fig 5 High m gnification sh wing the fine granular d po it which resulted from NADH D staini g in th h i cell l terna (Electron micrograph 100,000)

Fig 6 NADH D activity in hair cell mitocho d ia under highe magnificati n. The depositi n of f rmazan n th mitochondrial m mbranes i well hown. (Electron micrograph × 95,000)

PROCEDURES

1 The specimens were fixed in cold 6.25 hydroxyadipaldehyde or 4% formaldehyde with 8% sucrose in 0 1 *M* cacodylate buffer pH 6 for 30 minutes. After this prefixation the tissue was washed in several changes f 0 1 *M* cold cacodylate buffer pH 7.6 containing 8% sucrose for 2 hours. Then the material was incubated in the mixture designed for the demonstrating for SDH and NADH D activity for 20–30 minutes at room temperature

2. Without any prefixation the specimen was washed in cold 8 sucrose in 0 1 *M* phosphate buffer pH 7 for 15 minutes and incubated in the mixture described above for 20–30 minut s at room temperature



Fig. 10. Control incubation with formaldehyde prefixation. X mitochondrial st I ing occurred but som deposit occurred i the endoplasmic reticulum when the tissue was treated w th formaldehyde prior t incubation. (Electron micrograph 100,000)

NADH D acti ity is exhibited by portions of this membrane system The reacti ar are distributed in a patchy fashion (Figs. 4 and 5) Mitochondrial acti ity is completely inhibited if formaldehyde is used as prefixation but end plasmic reticulum staining withstands formaldehyde (Fig 10)

DISCUSSION

Impro ed histochemical technique for these two oxidati enzymes, SDH and NADH D, have simplified the problem of describing their distribu tion within the cochlea. Light microscopy reveals that the stria vascularis nd Deiter s cell are more reactive than hair cells. When their mito-

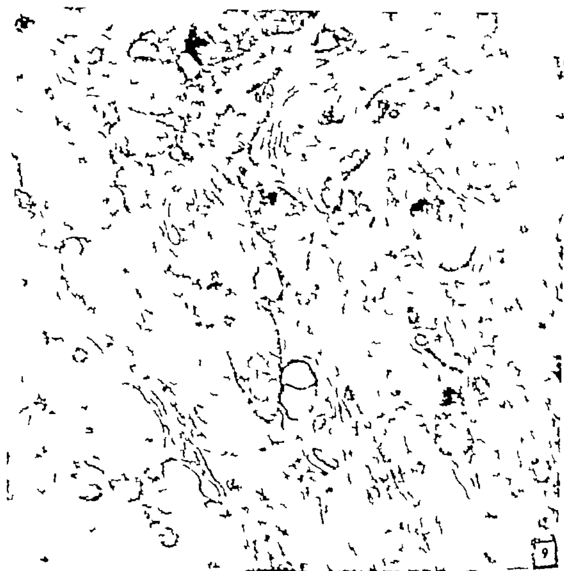


Fig 9 Co trol incubati n with ut ub trate tri ascularis. N staini g l evid nt D nse bodies are evident in ma y of the mitocho dria, but no precipit te f rmed. (Electron microgr ph 60,000)

As Figs 1 and 2 show the cells of the stria vascularis and Deiter's cells have more intense staining than hair cells as seen with the light microscope The pattern is quite similar for either SDH or NADH D The hairs of the hair cells often were the site of large aggregates and may be richly supplied with these enzymes Inner hair cell hairs were more reactive than other structures of the cochlear duct

Very fine granules appeared on the membranes of mitochondria with this technique The deposit occurred in a regular pattern on only the outer surface of the cristae (Figs 3 and 0) The mitochondria had a similar pattern of staining in every type of cochlear cell

A parallel array of membranes line the sides of hair cells. They are flat cisterns, which may be connected to the endoplasmic reticulum

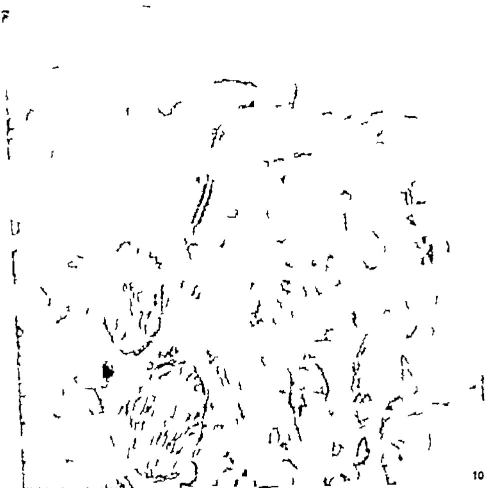


Fig 10 Control incubation ith formald h de prefixation. N mitochondrial stai ing occurred but same deposit occurred the ndopla mic reticul m when the tissue w treated ith formaldehyde prior t incubation. (Electron micrograph 100,000.)

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chondrial content is compared by electron microscopy it becomes apparent that the cells with more mitochondria exhibit greater enzyme activity (Figs 7 and 8) Biochemical studies of cellular fractions have showed that most oxidative enzyme activity occurs in mitochondria (Green *et al* 1954 Singer *et al* 1956 Watson & Siekevitz, 1956) No significant difference in staining characteristic emerged in this study between mitochondria from different areas except within the stria vascularis where dark or marginal cell mitochondria were more reactive than intermediate and basal layer cells. This apparent difference may be due to penetration factors.

Nutrition is provided indirectly to hair cells in the organ of Corti The high rate of oxidative metabolism of the supporting and stria vascularis cells is reflected by their content of mitochondria and these enzymes must be involved in this important role It may be interesting to speculate about the chemical substances that are received by the hair cells from their surroundings. A great deal of work has been done on the analogous problem of neuron nutrition by glial elements, but the fundamental questions still remain unanswered (Kuffler & Nicolls, 1966) One of the interesting sidelights of these studies regarding the relationship between neuron and supporting cells is the surprisingly high concentration of sodium in the glial cells (Zadunaisky *et al* 1965) In the future we will try to determine whether this same reverse sodium potassium intercellular content is present in cochlear supporting cells

There is a cistern system of parallel membranes oriented in the long axis of hair cells lining the outer wall along the side of the cells. ATP-ase activity was not obvious on the hair cell wall in this region (Nakai & Hilding 1967) The cistern membranes do have areas of oxidative enzyme activity as shown in Figs. 4 and 5 In our earlier paper we speculated that the parallel membranes were engaged in transporting substances along the long axis of hair cells. The presence of NADH D on portions of the membrane system may have some importance in its role within hair cells.

CONCLUSIONS

We used a formazan histochemical technique for studying the distribution of two oxidative enzymes, SDH and NADH D Generally the relative degree of staining between various types of cochlear cells can be correlated with their mitochondrial content The more mitochondria cells have the more obvious their staining when they are examined with light microscopy Within mitochondria, these enzymes are distributed on the outer surface of cristae.

ZUSAMMENFASSUNG

Jüngst entwickelte Formazan Methoden für die elektronenmikroskopische Lokalisation von SDH und NADH D enthullten weitere Einzelheiten über die Vertei

lung dieser Enzyme in der Cochlea Der Aktivitatsgrad w lcher sich in den erschiedenen Zellarten eigte korrellerte gut mit dem Mitochondriengehalt. Die Stria ascularis war sehr reaktiv Die Stutzzellen zeigten mehr Akti ität als die Haarzellen. Die Formazanmethode liess di genaue Lokalisation der Enzymaktivität auf der M tochondrienmembran erkennen. NADH D scheint in der Parallelmembran und im Zisternensystem, das si h longitudinal in den Haarzellen befind t, orhande zu sein

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Results

The history questionnaire responses were highly similar to the previously studied normals. However the behavioral effects observed in the present experiment were in general somewhat to considerably less severe in the LDs than in the normals.

No positional alcohol nystagmus was evidenced by any LD subject in either left or right lateral head positions.

To facilitate quantitative comparisons of present results in LD subject with previous results in the normals, the blood alcohol and ataxia test findings in both studies appear as a composite illustration (Fig. 1)

Visual rail walking was the only test on which LDs demonstrated performance decrements following alcohol administration (Fig. 1 B). Two hours after ingestion of 80-proof and three hours after ingestion of 100-proof vodka the baseline performance levels were surpassed. In both the 80-proof and 100-proof experiments the LDs were slightly less affected (mean loss of about 2 steps) than the normals (mean loss of 3 to 4 steps)

Although the magnitude of blood alcohol concentration was somewhat higher in LDs than in normals (Fig. 1 A) there was n corresponding increase in performance decrements

Because of the provocative finding of less magnitude and shorter duration of performance decrement in LD subjects than in normals, it was desirabl to repeat the xperiment using a similar group of LD subjects in an attempt to substantiate and expand on these findings.

EXPERIMENT II

For bette quantitati e (numerical) between-group comparison of magnitude effects on alcohol influenced ataxia test behavior three additional bilateral LD subjects, ages 25 3 and 38, were studied with the following hanges in experim ntal conditions (1) isual rail walking and isual rail tanding tasks were made easier by the use of wider rails to permit equatability of baseline performance scores with those of the normals (but not equatability of baseline vestibular-dependent abilities) and (2) on of the standardized nonvisual tasks performed on the floor—Sharpened Romberg (SR) test, was repeated

Methods

"Optimum width of rails for the walking and standing-with-eyes-open task were selected from the standardized Long Version of the rail battery (Graybiel & Fregly 1966) These were of sufficient width merely to permit se ral repeatable perfect scores during the morning and fternoon practice sessions held for four days immediately preceding the experimental day To each individually determined optimum rail were added several succes-

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ACUTE ALCOHOL ATAXIA IN PERSONS WITH LOSS OF LABYRINTHINE FUNCTION[1]

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The effect of alcohol on the postural equilibrium of seven persons with bilateral labyrinthine defects (LDs) was investigated mainly for the purpose of further elucidating the functional role of the vestibular organ in man. Generally, magnitude and duration of the intoxicating effects were found to be less than observed previously in normal persons. The superimposition of an acute alcohol ataxia on persons with pronounced, characteristic vestibular ataxia appears to depend on the degree to which they have compensated for their loss of vestibular function. To the extent that experimental conditions were comparable for both normal and LD subjects the vestibular organ may be regarded as a factor contributing to "acute alcohol ataxia" in normal persons.

Previous reports from this laboratory described a new quantitative ataxia test battery (Fregly & Graybiel 1966, Graybiel & Fregly 1966) and its use in measuring performance decrement in normal persons as a result of alcohol intoxication (Fregly *et al.* 1967). The present report describes the effects of alcohol intoxication on postural equilibrium in two groups of bilateral labyrinthine defective (LD) subjects.

EXPERIMENT I

Procedure

Subjects and methods

The participants were four males, 27, 33, 46 and 50 years of age who with others constitute a comprehensively studied group of LD subjects with nearly if not totally complete absence of vestibular function (Graybiel 1964, Graybiel 1965, Graybiel & Clark 1965, Graybiel & Johnson, 1963, Guedry 1965). All test procedures were identical to those employed previously with normal subjects (Fregly *et al.*, 1967).

[1] This study was conducted under the sponsorship of the Office of Advanced Research and Technology, U.S. National Aeronautics and Space Administration, Order No. R-93.
The opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

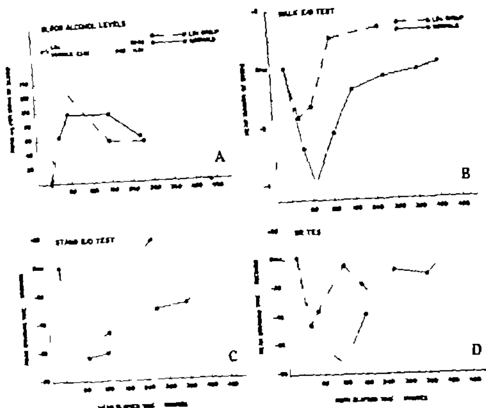


Fig. 2. Comparisons of 100-proof vodka effects in a group of three bilateral labyrinthine-defect subjects (JO, PE, and ZA) with a group of thirteen vestibular normal subjects: (A) Blood alcohol level; (B) rail walking with eyes open; (C) rail standing with eyes open; (D) standing on floor with eyes closed.

The over-all mean baseline performance scores shown in composite Fig. 2 represent the pre-experimental performances of the three LD subjects on their individually tailored rails (mean of 13.7 Walk Eyes Open steps and mean of 124.8 Stand Eyes Open seconds). Visual rail-walking performance decrements were again observed in the LDs (Fig. 2 B). The magnitude of the decrements, the rate at which maximum decrements occurred, and the onset and recovery periods were nearly identical to previous results despite the reduced level of difficulty of the task. In the normals (Figs. 1 B and 2 B) maximum decrement occurred later (70 minutes after alcohol intake versus 33–45 minutes in the LDs), the magnitude of maximum decrement was greater (mean loss of 4 steps versus a loss of only 2 steps in the LDs) and recovery was later (7 hours versus $2^1/_4$–3 hours in the LDs) under the influence of the 100 proof vodka.

But unlike the previous LD group, the second LD group showed visual rail-standing decrements; these were remarkably similar to those shown

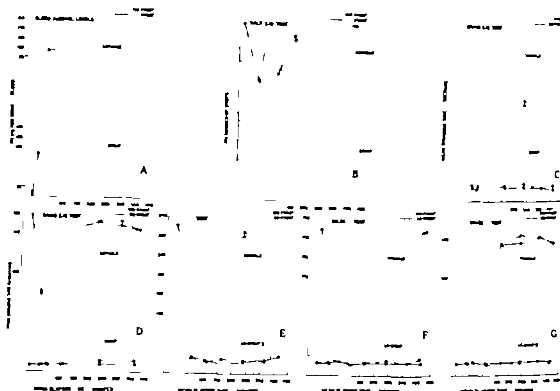


Fig 1 Compari ons of 80-proof a d 100-proof v dka ffects in a group f four bilat ral laby inthine-d fecti e subjects (DO, GR HA, MY) with a group of thirteen estibular n rmal subjects (A) Blood lcoh l level (B) walking w th eyes open n / inch-wide rail (C) standing with yes pen n th / inch rail (D) standing with eyes closed on n 2 / inch wid rail (E) standing on floo with ye losed (F–G) standing one l g (n floor with eyes closed)

sively narrow rails to provide a "top to each tailor made rail battery Within group differences in baseline performance scores were thus highly controlled each subject s baseline score representing a performance near his maximum, but of sufficient difficulty to yield a decrement under the experimental conditions All subjects also practiced the SR test as often as they did the rail battery

As before blood alcohol levels were determined [1] the drinking history questionnaire was administered and a log of the subjects behavior was kept Testing for PAN was not repeated because of negative findings in Experiment I

Results

The subjects accounts of the alcohol effects were limited to physical complaints. The uniform outstanding complaint was that of numbness.

[1] Blood was drawn from th a l be t the i t rval indic ted in Experiment I nd blood alcohol concentrations w re d t mined by microtech iq using gas hromatography (Colehour 1967)

DISCUSSION

That decrements in performances by the LD group in Experiment I were observed only on the visual rail-walking task is consistent with the finding that *visual rail-walking* was the *only* standardized task which was appreciably compensable for vestibular loss. On the visual rail-standing task and all of the nonvisual (floor and rail) tasks, the characteristic noncompensable losses shown pre-experimentally in these LDs were far greater than the severity of loss of visual rail walking skill i.e., performances were initially so poor as to prevent further decrement even with potent alcohol stimulation. The LD subjects scores on the five tests which were not influenced by alcohol in Experiment I not only were low but also similar (around 10 seconds per test or 3 seconds per trial) the scores made by the normal subjects on the identical tests under control conditions were 80 to 240 seconds per test, or 27 seconds to 60 seconds per trial. The "3-seconds" score seemed to be independent of factors causing differences in performance among normal subjects and among LD subjects on the partially compensable and, thereby less vestibular-dependent test—visual rail walking. This minimum, uniform score seemed to be dependent on an initial state of good equilibrium that could be maintained only briefly. If corrective postural mechanisms are called into play to maintain balance for 3 seconds, then our findings indicate alcohol does not influence them. If 3 seconds is too short a period effectively to call postural mechanisms into play then this represents a (initial) period which is not subject to testing.

On the wider rails and, thereby "easier tests" employed in Experiment II decrements were observed on both visual tasks. But despite maximization of between-group comparability of decremental effects in terms of better equatability of baseline scores, decreases in level of performance on visual rail walking skill were again found to be less in LDs than in normals. Smaller decrements in visual rail-standing performances, however did not obtain indeed, these decrements were slightly greater in the LD group than in the normal group. If this result is not attributable to between group differences in the baseline scores (the test was made somewhat too easy for the LDs and was not nearly so well equated with the normals as was the rail-walking test) and can be shown to be a reproducible finding under conditions of better equatability of baseline scores with those of normals, it might have theoretical significance in view of the different nature of these two tests. For example in the LD subjects the standardized Stand Eyes Open task performed on the 3/4 inch wide rail is more akin to the standardized non visual rail and floor tasks than to the Walk Eyes

The characteristic vestibular ataxia of the LDs is so intense that none was able to meet the minimum criterion for a scorable trial on the Walk A Line Eyes Closed Test (Fregly & Graybiel, 1968)

TABLE 1 *Influences of 100-proof vodka on the Sharpened Romberg Test performances of the three labyrinthine-defective subjects of Experiment II*

		Individual performances				
		Scores during alcohol stimulation				
Subject	Baseline score	34[a]	72	134	184	272
JO	18.7	11	1	19	12	16
PE	18.9	14	10	22	33	31
ZA	152.0	32	60	138	93	28

[a] Elapsed time in minutes since alcohol intake

by normals although only in terms of magnitude (maximum loss of 75 seconds in the LDs versus 62 seconds in the normals) (Fig 2 B) In the normals, maximum decrements in the visual rail standing occurred later (at 70 minutes after alcohol intake versus 33 minutes in the LDs) as did recovery of losses (7 hours versus 2 $^1/_2$ hours in the LDs) As with the previous LD group the performances on the visual tasks eventually surpassed the baseline levels

The alcohol effects on SR performances of two of the subjects, JO and PE (Table 1) were similar in magnitude to the effects seen in the LD subjects of Experiment I (Fig 1 E) although relative to the baseline scores the decrement was highly similar to that of the normals (33 per cent in these two LDs versus 31 per cent in the normals) A totally unexpected finding in the exceptional subject ZA was the outstanding improvement of his SR test performance during the practice sessions Thus the substantially higher SR baseline level of the present LD group (Fig 2 D) than of the previous LD group (Fig 1 E) was attributable almost entirely to ZA's improved performance But even subject ZA's baseline level (mean score of 152) was less than the alcohol-depressed SR level in the normals. As was found with the visual rail tasks maximum SR decrements occurred much sooner than in the normals Within the LD group subject ZA was least able to maintain his recovery (Table 1) His final score reverted to the level of maximum decrement due to alcohol, but this probably reflected his extreme drowsiness (he slept considerably between testing) in conjunction with a severe headache for which he required aspirin The SR performances of subjects JO and PE not only regained but surpassed their baseline levels

The blood alcohol levels of the LDs of Experiment II during the earliest periods of sampling (Fig 2 A) were quite similar to those calculated for the LDs of Experiment I (Fig 1 A) In the succeeding two periods of sampling the blood levels were more similar to those of the normals.

his counterrolling index is poorer than that of his cohorts (Graybiel, 1964). Thus all other testing of vestibular function to date indicates certain loss of canal function and extreme, if not total loss of otolith function in this subject. On the other hand, ZA was afflicted by meningitis considerably earlier in life than all except one of his cohorts, thus affording him a greater opportunity for nonvestibular proprioceptive sources of compensation for his labyrinthine defect. In addition, he is an individual with outstanding motor coordinative abilities for example he developed ballet skills at an early age. Present experimental findings therefore most likely reflect nonvestibular rather than vestibular origins of his improved SR performance and, thereby the source for the superimposition of an acute alcohol ataxia upon his previous pronounced vestibular ataxia.

The negative positional alcohol nystagmus finding corroborates findings with animals (de Kleyn & Versteegh, 1930) and both earlier results of a different experiment in this laboratory with some of these LD subjects (Harris *et al.*, 1962) and results of experiments elsewhere (Aschan *et al.*, 1956) which attempted to elicit PAN in an analogous group of bilateral labyrinthine-defective individuals. Inasmuch as unilateral vestibular function was found to be sufficient to elicit both phases of PAN (Aschan *et al* 1964) it would be worthwhile to try to determine the extent to which 1) residual unilateral vestibular function, and 2) residual bilateral function might be sufficient for the elicitation of PAN

Generally results of Experiment II support the results of Experiment I. Ability to compensate for poor performance skill on a nonvisual task was shown unexpectedly by one LD subject, seemingly due to outstanding utilization of nonvestibular (tactile-kinesthetic) cues in that individual. An additional finding in Experiment II was the disclosure that widening of rails to permit greater opportunity for nonvestibular processes underlying postural equilibrium to operate in the presence of pronounced vestibular ataxia provided, in turn, a greater opportunity to demonstrate the influences of alcohol on such processes.

If it is assumed that the experimental design was adequate, the between group differences in the alcohol effects on vestibular-dependent ataxia test behavior are accounted for by between-group differences in the integrity of the vestibular apparatus. On the strength of available evidence which argues strongly for overwhelming central nervous system effects of alcohol on behavior and on the assumption specifically that these effects are controlled at the reticular activating system level (Kalant, 1961) then our result may be interpreted simply as follows. In the LD subjects the markedly reduced, if at all functional, vestibular inputs to this central regulatory system were not added to the compound triad of inputs (vision, vestibular function, nonvestibular proprioception) vulnerable to alcohol and required for stringent maintenance of postural equilibrium hence the full effect of alcohol as observed in normal individuals were in a sense, short-circuited

Open task on the $^3/_4$ inch *rail*, and to the extent that these comparisons in test difficulty levels reflect differences in a) vestibular-dependency and b) nonvestibular sources of compensability for vestibular loss, the differential alcohol effect might well be a reflection of this differential

That improvements over baseline levels were noted in the LDs during both experiments may reflect either additional acquired compensation as a result of the oft repeated experimental testing or a rebound of activity of those structures suppressed by alcohol Such a rebound has been posited as the explanation of PAN reversal during the hangover period (Kalant, 1961) This pattern was not seen in the normal subjects, even on the task having considerable top in terms of difficulty (visual rail standing) Further investigation is required to determine whether the pattern is specific to LD subjects Extending the duration of the experiment coupled with the administration of a more difficult visual rail walking task might show similar results in normals

Since rate and extent of behavioral changes are functions of the rising blood alcohol concentrations (Kalant, 1961) the higher blood levels in the LDs than in the normals in both experiments (Figs. 1 A and 2 A) would reasonably be expected to reflect more rather than less decrements and slower rather than faster recovery than seen in the normals. The between group differences observed with LDs showing smaller Walk Eyes Open performance decrements in Experiments I and II and more rapid recovery on all three ataxia tests in Experiment II warrant the suggestion that loss of vestibular function lessens the alcohol effects upon the skills studied This finding may be attributable in part to a superiority of LDs over normals in using nonvestibular cues in difficult walking and standing tests.

Interpretation of the unexpected findings on subject ZA is dependent upon accounting for his startling improvement in SR test performance during the practice sessions In view of the nonvisual nature of the task such a high degree of compensation necessarily reflects either residual vestibular function a greater ability to compensate through nonvestibular functions than is generally considered possible (Gernandt 1964) or an interaction of residual vestibular function with utilization of nonvestibular cues Albeit so great a compensation by means of nonvestibular functions alone seems unlikely nevertheless a vestibular source of compensation either residual semicircular canal and/or otolith function, seems more unlikely ZA has failed repeatedly to show any objective or subjective vestibular responses to brief or sustained rotation (Graybiel 1964 and 1965 Graybiel & Johnson 1963 Guedry 1965) or to intense, sustained ice-water caloric stimulation[1] Moreover although he is one of the six LDs who have perceived the oculogravic illusion (Graybiel & Clark 1965) he no longer perceived the illusion when tested under water in another experiment (Graybiel *et al* 1967 Graybiel *et al* in preparation) Furthermore

[1] Unpublished data, 1966

la durée des effets into iquants étaient moins dans les personnes *normales qu'on avait observées auparavant*. La superposition d'une ataxie aigu d'alcool dans des personnes qui souffrent d'une ataxie caractéristique et prononcée dépend du degré a ec leq l ils ont *compensé la perte de la fonction* vestibulaire. Com parant tant que possible les conditions des expériments avec des personnes nor males et vec des personnes qui ont des déf uts bilatéraux *du labyrinthe* *on peut* dire que l'organ estibulaire est un facteur contribuant à l'at xie aiguë d'alcool dans des personnes norm les.

ZUSAMMENFASSUNG

Die Wi kung von Alkohol auf das Körpe liche Gleichgewicht bei Personen mit bilateralen Laby int Defekt n (LD) wurde untersucht, um weitere Aufklärungen f die Rolle die d estibulare Organ im Menschen spielt, *zu finden*. Im ll gemein n waren Bedeutu g und D ue de berauschenden Wirkungen geringer als die di man früher bei normalen Personen beobachtet hatte Da we t re Hin zufugen iner „akuten Alkohol-Ataxie bei Person n mit ausgesprochen charak terist scher estibularer Ata ie sch i t d on abzuhängen in welchem Masse sie de *Verlust ihrer vestibularen Funktion ausgeglichen haben*. Soweit die V rsuchs bedingungen fur normale Personen sowie fü solche m t bilateralen Labyrint Def kten ergleichbar waren, kann da vestibulare Organ al Fakt r angesehen werden, der zu einer „akuten Alkohol-Ataxie n normalen Personen beiträgt

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The further comparison of findings in LDs with previous findings in normals made clear the observation that the visual rail ataxia test items alone are sufficient to demonstrate significant adverse effects of moderate alcohol intoxication whatever the extent to which the performance skills thereon are vestibular-dependent. Thus, consistent with known CNS influences (Gernandt 1964) the alcohol effects on postural equilibrium were basic and generalized rather than specific to the vestibular system. Accountability of the findings in these terms would appear equally valid with respect to the ataxia test differences observed between normals and LDs following prolonged rotation (Fregly & Kennedy 1965) and following a severe storm at sea (Fregly & Graybiel 1965).

Insofar as the between group differences observed in our limited study of the qualitative behavioral changes due to alcohol can be shown to be reliable when studied as stringently as we have studied postural equilibrium then accountability on a vestibular basis, directly or indirectly, will have important theoretical implications in view, seemingly, of the unlikelihood of such accountability.

While alcohol influences on postural equilibrium functioning in our groups of subjects reinforce the important role of the vestibular organ in such functioning, elucidation of the basic role of nonvestibular proprioception during moderate alcohol intoxication, although considerably more problematic, requires investigation before the importance or weighting of the vestibular role *per se* in normal persons can become fully known.

CONCLUSIONS

The findings in this investigation permit the following conclusions.

1. The intactness of the vestibular organ may be regarded as a factor contributing to "acute alcohol ataxia" in terms of both the magnitude and duration of the ataxia.

2. An "acute alcohol ataxia" is superimposable on a pronounced vestibular ataxia only to an extent, apparently, that such ataxia becomes compensable via nonvestibular processes.

3. Qualitative behavioral changes in response to alcohol appear to be of lesser severity and duration in LD subjects than in normal subjects.

4. Positional alcohol nystagmus appears nonelicitable in individuals with total or nearly total absence of vestibular function.

RÉSUMÉ

Les recherches sur l'effet de l'alcool sur l'équilibre postural des personnes qui ont des défauts bilatéraux du labyrinthe ont pour but la clarification additionnelle de la fonction de l'organ vestibulaire d'homme. En général l'importance et

la durée des effets intoxiquants étaient moins dans les personnes normales qu on a it observées apparavant. La superposition d une ata le aigué d alcool dan des personnes qui souffrent d'une ataxie caractéristique et pro o cée dép nd du degré ec lequel ils ont compensé la perte de la fonction vestibulaire Comparant, tant que possible les conditions des expériments a ec des personn normales et ec des person es qui ont des défauts bilatéraux du labyrinthe on peut dire que l'organ vestibulaire est un facteur contribuant à l'ataxie igué d'alcool dan des personnes normales.

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Die Wi kung on Alkoh l uf das körperliche Gleichgewicht bei Personen mit bilateralen Labyrint Def kten (LD) wurde untersucht, um weit re Aufklärungen für die Rolle die das estibulare Organ im Menschen spielt zu finden. Im allgemeinen waren Bedeutung und Dauer der berauschenden Wirkungen geringer als die, die man früher bei n rmalen Personen beobachtet hatte D weitere Hinzufügen iner „akuten Alkohol-Ataxie bei Personen mit sgesprochen charakteristischer estibularer Ataxie scheint da o bzuhängen, in welchem Masse sie den Verlust ihrer vestibularen Funktion sgeglichen haben. Soweit die Versuchsbedingungen für n rmale Person n sowie fu solche mit bilateralen Labyrint Def kten vergleichbar waren, kann da estibulare Organ l Faktor angesehen w rden, der zu iner „akuten Alkohol-Ataxie" in normal n Personen beiträgt.

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CONCLUSIONS

The findings in this investigation permit the following conclusions

1 The intactness of the vestibular organ may be regarded as a factor contributing to acute alcohol ataxia in terms of both the magnitude and duration of the ataxia

2 An "acute alcohol ataxia is superimposable on a pronounced vestibular ataxia only to an extent, apparently that such ataxia becomes compensable via nonvestibular processes

3 Qualitative behavioral changes in response to alcohol appear to be of lesser severity and duration in LD subjects than in normal subjects

4 Positional alcohol nystagmus appears nonelicitable in individuals with total or nearly total absence of vestibular function

RESUME

Les recherches sur l effet de l alcool sur l équilibre postural des personnes qui ont des défauts bilatéraux du labyrinthe ont pour but la clarification additionnelle de la fonction de l organ vestibulaire d'homme En général l importance et

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COCHLEAR PATHOLOGY AFTER DESTRUCTION OF THE ENDOLYMPHATIC SAC IN THE CAT

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From the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Mass., U.S.A.

The endolymphatic sacs of the left ears of fifteen cats were destroyed surgically and after survival times of six months to three years, twelve were found to have endolymphatic hydrops. Four control ears which were subjected to sham operations and eighteen opposite ears failed to show endolymphatic hydrops. Three of four animals with post operative survival times of two and a half to three years also had atrophic changes in the organ of Corti and spiral ganglion which were most severe in the apical regions. Thus it appears that loss of function of the endolymphatic sac not only results in increase in volume of endolymph presumably due to inadequate resorption but also leads to atrophy of the sense organ and ganglion of the cochlea. A critical appraisal of all the evidence supports the concept that loss of function of the sac may be the primary etiologic factor in Menière's disease.

Endolymphatic hydrops has been of interest as a pathological entity since it was first described in 1938 by Hallpike & Cairns as being the principal histological finding in Menière's disease. Although the hydrops in Menière's disease usually occurs without other inner ear changes, as in our collection of 8 ears, Lindsay *et al.* (1952) recently have found degenerative changes in the organ of Corti and spiral ganglion in two of thirteen ears in their collection. The underlying disorder in Menière's disease appears to be an imbalance between secretion and resorption of endolymph resulting in an increase in volume of this fluid. On a purely morphological basis most investigators have assumed that the site of secretion of endolymph is the stria vascularis and possibly parts of the cristae, and that the site of resorption is the endolymphatic sac. This has led to a number of experimental attempts to produce hydrops by destroying the sac.

In 1947 Lindsay first attempted to establish a relationship between function of the endolymphatic sac and endolymph volume. He destroyed the sacs of seven monkey ears but failed to find hydrops after survival times of 3 months. In 195? Lindsay *et al.*, still not convinced that the endolymphatic sac had no function, performed a similar experiment on cats and

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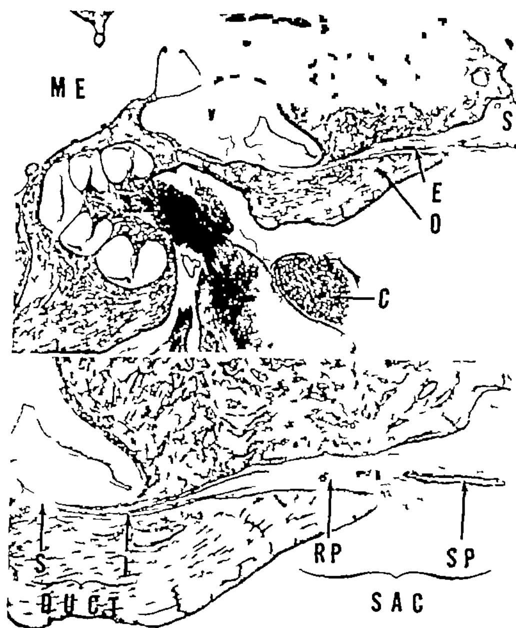


Fig. 1 A atomv f the nd lymphati duct a d sa f the at \bo ME, middl e r l estibul S lgm ld lnus E nd lymphati sa O perculum C, choroid ple us. Bel w S al u I l thm RP rug e porti n SP mooth port o

again failed to identify endolymphatic hydrops or other pathological changes after survival times of 3 to 9 months.

In an experiment on behaviorally conditioned cats Schuknecht & Kimura (1953) failed to find hydrops or hearing losses after destruction of the endolymphatic sacs and cochlear aqueducts, after survival times of four months and less. Re-examination of the inner ears of these animals, however, reveals mild endolymphatic hydrops in all specimens. The authors had been unwilling to accept this mild hydrops as a significant abnormality because of the lack of control ears.

TABLE 1 *Results of surgical destruction of the endolymphatic sac*

Postoperative survival time (years)	No. of animals		Endolymphatic hydrops		Cochlea lesions
	Unsuccessful procedure	Successful procedure	Yes	No	
½		3	3		
1		3	1	2	
1½		3	3		
2	1	2	1	1	
2½	2	1	1		1
3		3	3		2
	Operated controls				
2½	4			4	
	Opposite ears				
½–3	18			18	1

In 1963, Schuknecht & Seifi reported the findings in two cat ears with survival times of fifteen months following destruction of the endolymphatic sacs. In neither ear was there endolymphatic hydrops. However both showed unexplained atrophy of the organ of Corti and the spiral ganglion in the basal mm of the cochleas. These findings were sufficiently exciting to prompt us to perform a similar experiment with longer survival times. The present report, therefore, is based on an experiment which began in November 1962, and concerns the morphological changes occurring in the inner ears of cats surviving 6 months to 3 years following destruction of the endolymphatic sacs.

In the meantime Kimura & Schuknecht (1965) pursued the hydrops probl m in a controlled experiment on guinea pigs with short survival times and for the first time produced hydrops by destroying the endolymphatic sacs.

Even more recently in a report to the American Otological Society Kimura (1967) showed further that in guinea pigs the hydrops is progressive and that d generative changes occur in the organ of Corti and spiral ganglion, most se erely in the apical region in an incidence directly related to survival time

EXPERIMENTAL PROCEDURE

A group of twenty-two healthy adult cats were selected fo the study In eighteen animals the endolymphatic sac of the left ear was destroyed by surgical procedure while the remaining four animals served as controls. Th ighteen animals were divided into six groups of three each

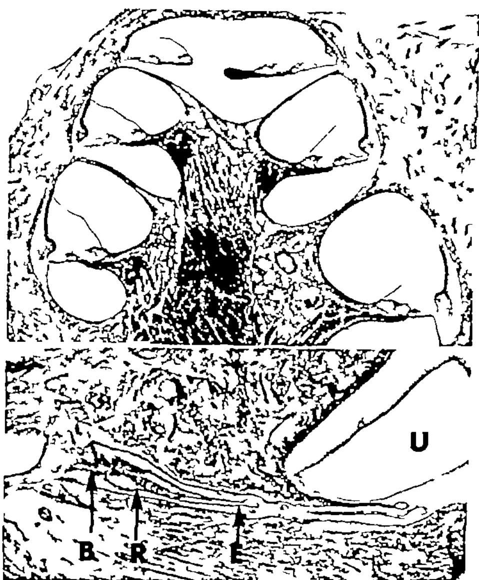


FIG. 2. Above: Absence of endolymphatic hydrops (Reissner's membrane in normal position) 2 1/2 years after partial destruction of the endolymphatic sac. Below: New bone (*B*) has replaced part of the sac but at least 30% of the rugose portion (*R*) remains. The endolymphatic duct (*E*) and utricle (*U*) are shown.

with post-operative survival times of 1/2 year, 1 year, 1 1/2 year, 2 years, 2 1/2 years, and 3 years respectively. The four control animals were subjected to a sham surgical procedure without destruction of the endolymphatic sac and all had survival times of 2 1/2 years.

The operative procedure was performed with the animal deeply anesthetized with Pento-barbital Sodium injected intraperitoneally. Utilizing aseptic technique, an occipital craniotomy was performed on the left side. The dura was incised, cerebrospinal fluid aspirated, and the cerebellum was retracted medially. The endolymphatic sac was identified and the operculum (Fig. 1) was drilled away with a 1 mm sharp cutting burr. The

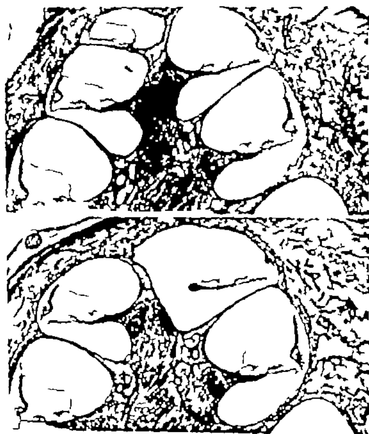


Fig. 3. Above: Mild endolymphatic hydrops 6 months after surgical destruction of the endolymphatic sac. Below: Slightly greater endolymphatic hydrops in another animal 2 years after destruction of the sac.

vestibular aqueduct was identified and as much was drilled away as was technically feasible without opening the common crus or vestibule. Gelfoam was placed into the surgical defect, the dural margins were approximated, and the scalp incision was closed with catgut suture.

A similar left occipital craniotomy was performed in the control animals. The cerebellum was retracted for a similar period of time and the superior and posterior surfaces of the petrous bone were subjected to a superficial drilling procedure while avoiding injury to the endolymphatic sac. For all twenty-two animals the right ears served as further controls.

The cats were killed by arterial perfusion with Heidenhain-Susa solution while deeply anesthetized with Pento-barbital Sodium. The temporal bones were removed en block with the basis occiput intact and were prepared in anatomical continuity. They were decalcified in Trichloroacetic acid, dehydrated in alcohols, embedded in celloidin, serially sectioned, stained with hematoxylin and eosin and mounted on glass slides.



FIG. 4 This ea sh wa almost total loss f hair cells and spiral ganglion cell in a 6 mm region of th apex 2 / y ars fte destruction of th nd lymphatic sac. There lso was 3 mm lesion at the basal end f the cochlea

RESULTS

The endolymphatic sacs were successfully destroyed and the specimens prepared without significant artefact in fifteen of the eighteen experimental ears (Table 1) The ears of one animal of the 2 year group had tears of the membranous labyrinth due to improper histologic technique which made assessment of ante mortem pathology unreliable The surgical procedure was unsuccessful in two of the 2 1/ year animals In one of these the posterior semicircular canal and common crus had been inadvertently opened during the operative procedure and in the other the sac was only partly destroyed (Fig 2)

Endolymphatic hydrops was present in twelve of the fifteen experimental ears in which the endolymphatic sac had been completely destroyed There was no evidence of endolymphatic hydrops in two of the experimental ears of the 1 year group and one of the experimental ears of the 2 year group No endolymphatic hydrops could be identified in the opposite ear of any of these animals or in the ears of the four control animals

The hydrops consisted f mild to moderate displacement of Reissner s membrane towards the scala vestibuli throughout all turns of the cochleas (Fig 3) The magnitude of displacement was less in the -year animals than the 2 year animals but did not progress from the 2nd to the 3rd year

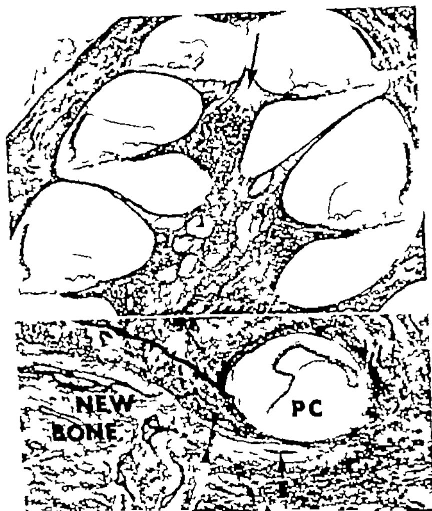


Fig. 5. Histological findings 3 years after destruction of the endolymphatic sac. Above: Moderate endolymphatic hydrops of the cochlear duct and atrophy of the spiral ganglion (arrow) in the apical region. Below: The endolymphatic duct (*E*) is blocked (arrow) by new bone near the posterior semicircular canal (*PC*).

after surgery. In none of the ears was there distention of the saccule, utricle or semicircular canals.

The organ of Corti and other structures of the cochlear duct, as well as the spiral ganglion, appeared normal in twelve of the fifteen ears in which the endolymphatic sac was successfully destroyed.

In one successfully operated ear of the 2 $^1/_2$-year group, there was severe degeneration of both the organ of Corti and spiral ganglion in a 3 mm region of the basal end of the cochlea, as well as in a 6 mm region of the apex, while the intervening portion of the cochlea appeared normal (Fig. 4).

Two of the animals in the 3-year group had cochlear lesions. One con-

sisted of degeneration of the organ of Corti and spiral ganglion in a 5 mm region of the basal end of the cochlea and the other in a 1 mm region of the apex of the cochlea (Fig 5)

Thus it appears that loss of function of the endolymphatic sac not only results in increase in volume of endolymph presumably due to inadequate *resorption of fluid but also leads* to atrophy of the sense organ and ganglion

There was degeneration of the organ of Corti and spiral ganglion from the 7 to 10 mm region of the unoperated ear of one control animal

CONCLUSION

The endolymphatic sacs of the left ears of fifteen cats were destroyed surgically and after survival times of 6 months to 3 years and twelve were found to have endolymphatic hydrops. Four control ears which were subjected to sham operations and eighteen opposite ears failed to show endolymphatic hydrops. Three of four animals with post-operative survival times of 2 1/2 to 3 years also had atrophic changes in the organ of Corti and spiral ganglion, which were most severe in the apical regions

The findings are consistent with those of Kimura who has produced both hydrops and cochlear lesions in guinea pigs, following destruction of the endolymphatic sacs

Recent studies by Lindsay *et al* have shown atrophy of the organ of Corti and spiral ganglion in two of thirteen human ears with Meniere's disease

Thus it appears that loss of function of the endolymphatic sac not only results in increase in volume of endolymph presumably due to inadequate resorption but also leads to atrophy of the sense organ and ganglion of the cochlea A critical appraisal of all the evidence supports the concept that loss of function of the sac may be the primary etiologic factor in Menière's disease

ZUSAMMENFASSUNG

Der Saccus endolymphaticus des linken Ohres wurde in fünfzehn Katzen chirurgisch zerstört. Bei zwölf Tieren wurde nach einer Überlebungszeit von sechs Monaten bis drei Jahren ein endolymphatischer Hydrops festgestellt. Vier Kontrollfälle wie auch die achtzehn gegenseitigen nichtoperierten Ohren zeigten keinen endolymphatischen Hydrops. Drei aus vier Tieren mit einer Überlebungszeit von zweieinhalb und drei Jahren wiesen auch atrophische Veränderungen im Cortischen Organ und Ganglion spirale vor die im apikalen Teil am schwersten waren Es scheint deswegen dass der Funktionsausfall des Saccus endolymphaticus nicht nur eine Endolymph-Volumenzunahme verursacht was der inadäquaten Resorption zuzuschreiben sein kann sondern auch eine Atrophie des sensorischen Organ und des Ganglion der Cochlea verursachen kann Eine kritische Auswertung der bisherigen Befunde unterstützt das Konzept dass der Funktionsausfall des Saccus endolymphaticus der primäre ethiologisch Faktor in Menièrischer Krankheit sein konnte

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MONAURAL FREQUENCY DISCRIMINATION IN SUBJECTS WITH MENIÈRE'S DISEASE

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The described technique for measuring DLF gave group mean values on normal subjects comparable to the group mean values of studies by other authors on normal subjects. The group mean values for DLF in subjects with Menière's disease are substantially greater than the same values for normal subjects and the same relationship is true for the standard deviations of the two groups. DLF in Menière's subjects is inversely related to stimulus intensity and shows the greatest separation from normal at the higher frequencies. Pitch discrimination (DL/F) 100 and dispersion of results, (SD/F) 100 show the lowest values at 4000 cps for the Menière's group as compared to 2000 cps for the normal group. This, when considered with the tendency for low tone threshold loss, would seem to implicate the upper middle and apical region of the cochlea as the site of greater involvement in Menière's disease. The frequency discrimination studies described in this paper are in no way a clinical test for Menière's disease.

Careful evaluation of the auditory symptoms in patients with Menière's disease frequently calls attention to aberrations of pitch perception both monaural and binaural. Both examiner and patient are more apt to be aware of the "diplacusis binauralis" than they are of the monaural pitch aberration since the latter is somewhat masked by the presence of intensity distortion (recruitment and aural overloading) and changes in timber of acoustic stimuli.

Extensive research has been done on intensity distortion (the recruitment phenomena) in various types of lesions of the auditory nerve and cochlea in general and in Menière's disease in particular. Relatively few studies have been done on the characteristics of monaural pitch distortion in Menière's disease. Meurman (1954) studied a group of 19 ears with Menière's disease and determined the difference limens for frequency (DLF) at 20 dB in

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tensity above threshold by a frequency modulation technique and compared the results with a group of 93 normal ears. He found consistent differences between the DLF in the normal ears and in the diseased ears at all frequencies (125 cps through 4000 cps) with no overlapping of the ranges at 125 500 and 1000 cps.

While the frequency modulation or warble technique tests something that is related to the ability of the ear to discriminate frequency the question can be raised as to whether it specifically tests the true difference limen for frequency as pointed out by Harris (1948)

In this study we have chosen a frequency matching technique utilizing two separate stimulus tones separated in time Many of the published sets of data on frequency discrimination in normal ears have been obtained under pure laboratory conditions where subjects are available for training and repeated testing to insure optimum results from each individual In this study the subjects with Menière s disease were patients from a busy otology clinic so that economy of time was an important factor The patient was able to submit to the test procedure on one occasion only It was anticipated that the data gath red in this way would be suitable primarily for comparison of group mean values rather than comparison of the data of an individual of one group with those of another group, since the range of results in untrained individuals would be too great. It is the purpose of this in estigation to describe a technique for measuring monaural pitch discrimination suitable for the above-mentioned clinical conditions to evaluate the results in a group of normal control subjects to compare the mean values with those of other authors in order to check the validity of our mean alues on normal subjects and finally to use this technique in a group of subjects with Menière s disease and evaluate the difference in monaural frequency discrimination ability between the diseased ears and normal ears.

Frequ ncy Discrimination in Normal Ears

The subject for the study of normal monaural difference limen for frequency were chosen from a group of employees at the Cleveland Clinic The criteria for selection were normal hearing (at least audiometric 0 dB at all frequencies tested) age (selected to pro ide representatives of each decade between 20 and 60 years) and intelligence sufficient to understand the test procedure

The study includes 50 persons, 30 women and 20 men, distributed in th various decades as f llows from 18 through 29 years of age (25 per sons) from 30 through 39 years of age (12) from 40 through 49 years (10) and from 50 through 59 years (3) The median age was 28 and the average 32 years.

All intensity lues in this paper are expressed according t the ASA scale.

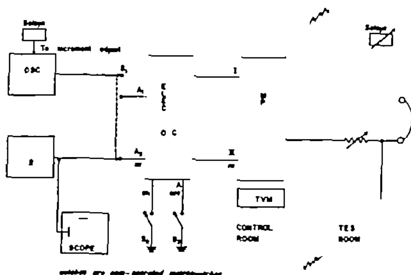


FIG. 1 Block diagram f equipment.

Description of Equipment

The equipment used for the study (Fig 1) included two General Radio beat frequency oscillators, Model 1304B one variable and one fixed The variable generator was equipped with two selsyn motors. One selsyn motor was attached to the cycle increment dial of the variable oscillator and was activated by the subject s manipulation of an unmarked dial on the second selsyn motor The cycle increment dial of the variable tone oscillator was modified so that there was a 300-cycle range on either side of the 0 cps marking Thus, the subject had a range of 600 cps in which to determine the pitch match The frequencies from the oscillator were fed into a *Grason–Stadler* electronic switch with *a modification using cam-operated* microswitches The electronic switch then fed the frequency from each oscillator separately at a specified time interval into the amplifier of a Grason–Stadler speech audiometer Model 162 which in turn amplified the frequencies and fed them into the test ear through a telephonic TDH-39-10Z headphone The interval between the constant tone and the variable tone was 0.25 second the interval between each pair of tones was one second *and the duration of each tone was one second The frequency under* test was checked by using a Hickok Model 670A oscillograph

Description of Test and Test Procedures for Normal Subjects

Each subject was given a pure tone audiometric test in which a Maico Model 1 audiometer was used to determine pure tone thresholds A General Radio beat frequency *oscillator and a Grason–Stadler* speech audiometer were used to determine auditory threshold for the test equipment Frequencies used in difference limen testing were *250 500 1000 2000 and*

Table I *Frequency DL—whole sample normal subjects*

DL Difference limen of frequency as measured by the mean deviation from the test frequency; S.D. standard deviation of the mean deviation; (DL/F) 100 = relation of DL of frequency in per cent (S.D./F) 100 = relation of S.D. of frequency in per cent.

Test frequency (cps)	*Observation*	Intensity above threshold, dB 10	40	80	Average for all intensities
250	DL in cps	2.0	1.8	2.0	1.9
	S.D. in cps	1.6	1.5	2.5	1.9
	(DL/F) 100	0.8	0.70	0.80	0.76
	(S.D./F) 100	0.6	0.61	1.00	0.74
500	DL in cps	3.2	3.2	3.5	3.3
	S.D. in cps	2.2	2.1	2.8	2.7
	(DL/F) 100	0.65	0.62	0.70	0.66
	(S.D./F) 100	0.65	0.62	0.55	0.61
1000	DL in cps	4.8	5.2	4.8	4.9
	S.D. in cps	3.1	5.1	4.6	4.3
	(DL/F) 100	0.48	0.51	0.48	0.48
	(S.D./F) 100	0.31	0.31	0.56	0.42
2000	DL in cps	8.9	7.8	7.8	8.2
	S.D. in cps	5.8	4.9	5.3	5.3
	(DL/F) 100	0.45	0.39	0.39	0.41
	(S.D./F) 100	0.29	0.25	0.26	0.27
4000	DL in cps	22.3	18.5	26.6	22.5
	S.D. in cps	20.7	19.3	23.0	21.0
	(DL/F) 100	0.56	0.46	0.66	0.56
	(S.D./F) 100	0.51	0.48	0.27	0.42

4000 cps. Tests of difference limen for frequency were given at the following intensities above each subject's threshold of hearing 10 40 and 80 dB Three matches were recorded in each intensity and a total of nine matches was made for each frequency

The subject was instructed in the purpose of the test and told that he would hear two tones, one constant and one variable, separated by an interval of silence He was instructed in the operation of the dial used in controlling the variable tone and asked to match the variable tone with the tone that remained constant No time limit was placed on the test but each subject was asked to match the two tones as quickly as possible yet still be fully satisfied with his match before stopping. When he was satisfied with his choice he was told to tell the examiner Monaural difference limen for frequency was recorded by turning the small increment dial of the constant tone oscillator until the oscilloscope matched the frequency of the variable tone oscillator Initially each subject was given a trial test using 1000 cps at 40 dB above his auditory threshold. This trial lasted until the subject was *completely* acquainted with the test procedure. After the

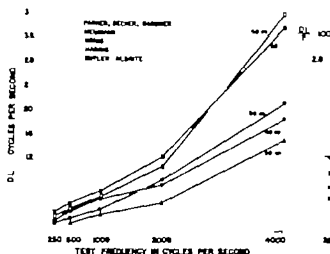


Fig 2

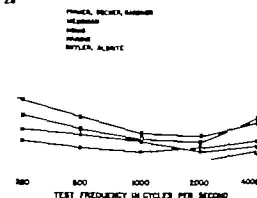


Fig 3.

Fig. 2 Difference limens for frequency for normal subjects compared with those reported by four other investigators.

Fig. 3 The curves of Fig. 2 converted to relative pitch discrimination as indicated by the percentage ratio (DL/F) 100

trial period the test of monaural difference limen for frequency was started The sequence for the frequencies tested was as follows 1000 2000 4000 500 and 250 cps There was a 10-minute rest period after each one-half hour of testing

Statistical Analysis

The following statistics were compiled the mean deviation of the matches from each test frequency (difference limen for frequency) the standard deviation of each mean deviation the factor (DL/F) × 100 the factor (S.D /F) × 100 and the significance of difference between the normal ears and the pathologic ears described in the second part of the paper

The first four statistical computations were also done for intensities of 10 40 and 80 dB The formulas used are

Mean $m = \frac{\sum xf}{n}$

Standard deviation $s = \sqrt{\frac{\sum x^2 f}{n} - \left(\frac{\sum xf}{n-1}\right)^2}$

Significance of difference between two sample means $= \frac{m1 - m2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$

Results in Normal Ears

The results of the DLF studies for the whole sample of normal ears are given in Table 1 for three intensities The DL for 40 dB is graphically illustrated in Fig 2 together with the curves reported by four other authors.

Table 2. *Frequency DL—musically trained and not musically trained subjects at 40 dB intensity*

DL Difference limen of frequency measured by the mean deviation from the test frequency s.d.—standard deviation of the mean deviation (DL/F) 100 = relative DL of frequency in per cent; (s.d./F) 100 = relative s.d. of frequency in per cent.

Test frequency (cps)	Observation	Musically trained	Non musically trained	Whole sample
250	DL in cps	1.5	2.3	1.8
	s.d. in cps	1.3	2.5	1.5
	(DL/F) 100	0.60	0.92	0.70
	(s.d./F) 100	0.52	1.00	0.60
500	DL in cps	2.8	4.3	3.2
	s.d. in cps	1.9	4.7	3.1
	(DL/F) 100	0.58	0.86	0.62
	(s.d./F) 100	0.38	0.94	0.62
1000	DL in cps	4.7	6.4	5.2
	s.d. in cps	3.4	8.0	5.1
	(DL/F) 100	0.47	0.64	0.51
	(s.d./F) 100	0.34	0.80	0.51
2000	DL in cps	6.7	10.2	7.8
	s.d. in cps	4.2	5.2	4.9
	(DL/F) 100	0.33	0.51	0.39
	(s.d./F) 100	0.21	0.26	0.25
4000	DL in cps	15.6	24.1	18.3
	s.d. in cps	12.9	28.2	19.3
	(DL/F) 100	0.38	0.60	0.46
	(s.d./F) 100	0.32	0.70	0.48

The results compare favorably considering the method and purpose of our technique. The standard deviations for each frequency are considerably larger in our group than those for the other authors. This is to be expected, as mentioned previously because of the absence of training in our subjects. Our results compare favorably enough with those of other investigators to justify the use of mean values gained by the technique for comparison with mean values of groups of pathologic ears.

It is evident from the curves in Fig. 2 that a difference limen for frequency increases steadily as the test frequency is increased and increases precipitously above 2000. This, however, is not a measure of pitch which is the subject's interpretation of stimulus frequency. Since an interval of a given number of cycles per second does not give the same subjective pitch interval at various points in the audible frequency scale and since equal pitch intervals (octaves) double in cycles per second as we go up the frequency scale the percentage ratio (DL/F) × 100, is more closely related to subjective pitch sensation than is the simple difference limen

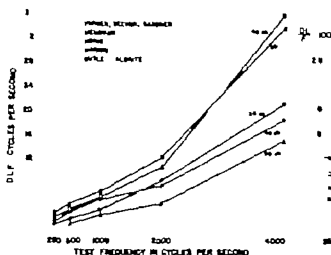


Fig. 2.

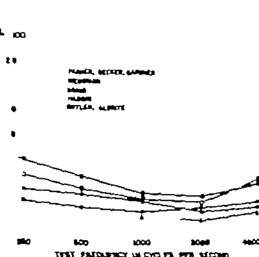


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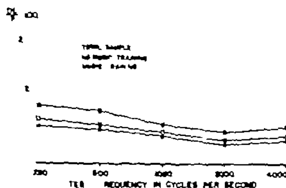
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Test frequency (cps)	Observation	Musically trained	Non musically trained	Whole sample
250	DL in cps	1.5	2.3	1.8
	s.d. in cps	1.3	2.5	1.6
	(DL/F) × 100	0.60	0.92	0. 0
	(s.d./F) × 100	0.52	1.00	0.60
500	DL in cps	2.8	4.3	3.2
	s.d. in cps	1.9	4.7	3.1
	(DL/F) × 100	0.56	0.86	0.62
	(s.d./F) × 100	0.38	0.94	0.62
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	(DL/F) × 100	0.47	0.64	0.51
	(s.d./F) × 100	0.34	0.80	0.51
2000	DL in cps	6.7	10.2	7.8
	s.d. in cps	4.2	5.2	4.9
	(DL/F) × 100	0.33	0.51	0.39
	(s.d./F) × 100	0.21	0.26	0.25
4000	DL in cps	16.6	24.1	18.5
	s.d. in cps	12.9	28.2	19.3
	(DL/F) × 100	0.38	0.60	0.46
	(s.d./F) × 100	0.32	0.70	0.48

The results compare favorably considering the method and purpose of our technique. The standard deviations for each frequency are considerably larger in our group than those for the other authors. This is to be expected as mentioned previously because of the absence of training in our subjects. Our results compare favorably enough with those of other investigators to justify the use of mean values gained by the technique for comparison with mean values of groups of pathologic ears.

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Fig. 4

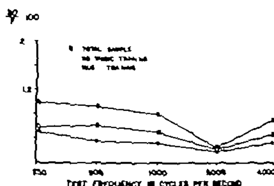

Fig. 5.

Fig. 4 Relative pitch discrimination curves for the entire sample compared with musically trained and musically naive groups (40 dB intensity)

Fig. 5 Relative dispersion of the DLF for the normal subjects (total sample, musically trained group and musically naive group as measured by (s.d./F) × 100 dB intensity

for frequency The four curves in Fig 2 are expressed as this ratio in Fig 3 These curves indicate that actual subjective pitch discrimination is most accurate in the area of 1000 and 2000 cps

Statistical analysis of the results of different intensities (10 40 and 80 dB) did not show any consistent differences at the various frequencies for the three groups with our testing technique The normal group was divided into two subgroups those subjects who had musical training or orientation and those who had no musical training or interests The data for these two subgroups (tested at 40 dB intensity) are given in Table 2 and the factor (DI /F) × 100 is plotted against test frequency in Fig 4 It is clear from these results that subjects with musical training or background had consistently better frequency and pitch descrimination ability than did those without musical training or background The relative dispersion, (s.d. /F) × 100 as shown in Fig 5 is much less for the musical individuals and illustrates, as would be expected, that musical training is an important factor in discrimination ability and accuracy in frequency studies It is of interest to note in Fig 5 that the dispersion of results is less for both groups in the area of 2000 cps where pitch discrimination ability was also found to be most accurate according to the results shown in Figs 3 and 4 This corresponds to the area of greatest sensitivity to stimulus intensity at threshold as indicated in the curves of threshold audibility of Sivian and White (1933)

Monaural Frequency DL in Pathologic Ears

Subjects for this group consisted of patients with the clinical diagnosis of Menière's disease who were willing to give several hours of time for the necessary testing The clinical diagnosis was made on the following basis (1) a history of episodic true vertigo tinnitus and hearing loss

TABLE 3. *Frequency DL—subjects having Menière's disease*

DL Difference limen of frequency as measured by the mean deviation from the test frequency; s.d. = standard deviation of the mean deviation (DL/F) 100 = rel U DL of frequency (per cent); (s.d./F) 100 = rel U s.d. of frequency (per cent).

Test frequency (cps)	Observation	Sensation level above threshold, dB			Average for all intensities
		10	40	80	
250	DL in cps	8.3	7.4	3.3	6.4
	s.d. in cps	14.3	10.5	4.5	9.8
	(DL/F) 100	3.4	2.9	1.3	2.5
	(s.d./F) 100	6.7	4.2	1.9	3.9
500	DL in cps	16.2	21.2	7.2	14.5
	s.d. in cps	28.0	48.2	11.4	29.4
	(DL/F) 100	3.0	4.3	1.4	2.8
	(s.d./F) 100	5.7	9.6	2.3	5.9
1000	DL in cps	18.1	20.5	24.2	21.0
	s.d. in cps	35.4	38.8	49.6	41.3
	(DL/F) 100	1.8	2.1	2.4	2.1
	(s.d./F) 100	3.5	3.9	5.0	4.1
2000	DL in cps	40.5	32.3	26.2	33.1
	s.d. in cps	66.7	52.6	42.6	54.0
	(DL/F) 100	2.0	1.6	1.3	1.6
	(s.d./F) 100	3.4	2.6	2.1	2.7
4000	DL in cps	63.4	64.0	44.3	57.9
	s.d. in cps	85.3	94.1	67.7	82.4
	(DL/F) 100	1.6	1.7	1.1	1.5
	(s.d./F) 100	2.1	2.2	1.7	2.0

usually of fluctuating nature often associated with a sensation of fullness, hyperacusis, and diplacusis (2) objective findings of a perceptive deafness either affecting the low tones primarily or affecting all frequencies from 125 cps to 8000 cps, and recruitment in at least one frequency (usually 1000 cps).

This group is made up of 20 patients, 9 women and 11 men, from 22 through 72 years of age averaging 47 years of age. There were three subjects from 20 through 39 years, six from 40 through 49, eight from 50 through 59 and three from 60 through 72 years of age.

Equipment and Test Procedures

The equipment used for testing of the patients with Menière's disease was the same as that described for the group having normal ears, and the test procedure was basically the same with the following modification: instead of conducting the test at intensity levels of 10, 40 and 80 dB above

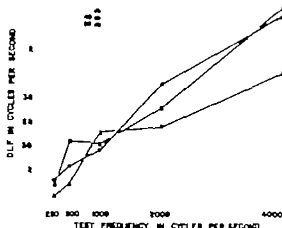


Fig. 6

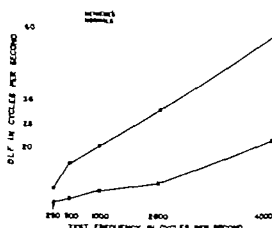


Fig. 7

Fig. 6 Difference limen for frequency for three sensation levels above threshold for the ears with Menière's disease (10, 40 and 80 dB)

Fig. 7 Comparison of the difference limen for frequency of the Menière group with the normal group, averaging all intensities for both groups

threshold it was conducted at sensation levels of 10 40 and 80 dB above threshold Therefore an alternate binaural loudness balance test was conducted in each frequency to find the appropriate sensation level at which to conduct the frequency discrimination test The test was then conducted in a manner identical to that for the normal group

RESULTS

Intensity relationship

The results for the whole sample of pathologic ears are given in Table 3 Individual curves for the difference limen for frequency at the three sensation levels 10 40 and 80 dB are presented in Fig 6 Although the differences between these sensation levels are not consistent at all frequencies, the smallest deviations are found at the 80 dB level in all frequencies but 1000 cps.

This inverse relationship between intensity and frequency discrimination ability in normal ears has been pointed out by previous authors (Schubert, 1957 König, 1957 and others) In this connection it is of interest to note that the best frequency DL's shown in Fig 2 were those done at the highest intensity level above threshold (90 dB) The presence of this relationship in an ear with Menière's disease is somewhat unexpected in view of the overloading characteristics of the cochlea in this disease as shown by Lawrence & Yantis (1956) In our group of pathologic ears, the 80 dB sensation level at 1000 cps averages 26 dB above threshold Yet the mean overloading intensity for ears with Menière's disease in Lawrence & Yantis series for 1000 cps was 13 dB above threshold Thus, the majority

TABLE 4. *Significance of difference between DLF's for normal ears and ears with Menière's disease*

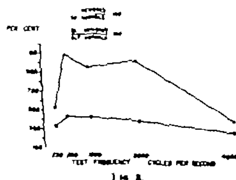
Test frequency cps	Confidence lev l,	Z^*
250	100	5.1
500	100	4.9
1000	100	5.0
2000	100	6.0
4000	100	5.5

100% Confidence lev l = Z 3.00.

of ears in our group at 80 dB sensation levels should be overloaded It might be expected that the presence of aural harmonics would interfere with the DLF and yet, the intensity relationship found in normal ears still holds. Davis and associates (1950) and Schubert (1957) have shown that pitch displacement in noise-damaged ears also decreases with increasing intensity It, therefore seems apparent that pitch aberrations in inner ear disease are lessened by increasing intensity

Frequency relationships

The DLF's for all intensities averaged together in the pathologic groups are plotted against the same data for the normal group in Fig. 7 It is lear from this gr ph that there is a substantial difference between the DLF' in the two groups at all frequencies. In Fig. 8, the DLF for the



F1g. 8.

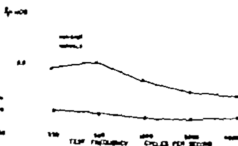


Fig. 9.

Fig. 8 Differe nce l mens for frequency for the Menière group plotted as percentage f the difference limens for frequency of the normal group, nd standard deviations of the Menière group plott d as percentage of the standard deviations f the normal group erag of all i tensities)

Fig. 9 Relati pit h discrimination curv for Menière group compared with that f the normal group as measured by (DL F) 100 (ll intensities erag)

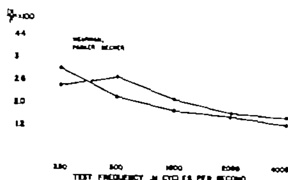


Fig 10

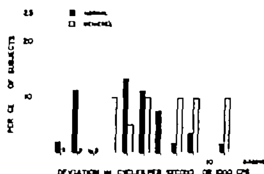


Fig 11

Fig. 10 Relative pitch discrimination curves for the data of the Menière group in this study compared with the same data of Meurman's study measured by (DL/F) 100. (Meurman study 20 dB intensity level above threshold; our study average of 10, 40, and 80 dB sensation levels above threshold.)

Fig. 11 Frequency of individual deviation at 1000 cps of the normal group compared with that of the Menière group (average of all intensities to both groups).

Menière's group is calculated as a percentage between the two DL's. Calculation of the significance of difference between the two sample means at each frequency gives a number which falls within 100% confidence level (Table 4). The percentage relationship of the standard deviations of the pathologic group as compared with the normal group is also illustrated in Fig 8. The extreme difference in this case illustrates well the difficulty and inaccuracy of pitch discrimination in ears with Menière's disease. In Fig 9 the factor $(DL/F) \times 100$ is plotted for the normal and abnormal groups. It should be noted that the lowest value for the diseased ear is at 4000 cps, whereas the lowest values in the normal groups are at 2000 cps (Figs 3, 4 and 5). The percentage difference values in Fig 8 are also lowest at 4000 and Meurman's (1954) values are also lowest at 4000 for the ears with Menière's disease in his series. Meurman's values agree essentially with ours with minor differences (Fig 10).

It seems clear from the above data that in Menière's disease the greatest alteration of pitch discrimination ability is in the low tones as measured by the DLF/F and that the accuracy of frequency matching as measured by the standard deviation is relatively worse in the low tones. The smallest difference limens for pitch and the most accurate matching are done at 4000 cps as opposed to 2000 cps for the normal subjects. This greater involvement in the lower part of the frequency range corresponds to the greater loss of threshold sensitivity in the lower frequencies in Menière's disease, particularly in the early and less severe cases.

Schuknecht & Neff (1952) have shown that lesions of the apical and upper middle region of the cochlea produce loss of threshold sensitivity in the low frequency ranges. Tasaki (1954) has shown that nerve fibers from the apex respond to low tones and that fibers from the basilar region

respond to both low and high tones. The correlation of the preceding audiometric data with the localization of function as presented by Schuknecht & Neff and Tasaki, would seem to implicate the upper middle and apical region of the cochlea as the site of more severe disease in Menière's disease, particularly in early cases.

Range

In spite of the tremendous difference in mean values between the normal and pathologic groups, the dispersion of individual deviations is such that there is considerable overlapping of the ranges of the two groups so that one cannot predict with accuracy from the data of any individual, whether that individual would have a normal ear or a pathologic ear. The least overlapping in ranges between the DFL for the normal group and that of the Menière group occurs at 1000 cps. This is demonstrated in the bar graph in Fig. 11 where the percentage of subjects having a given deviation is plotted. At this frequency 87 % of the deviations for normal are 7 cps and below and 75 % of the deviations in the Menière group are 8 cps and above. Thus, in our study any ear with a monaural DFL of 8 cps or above would have approximately an 80 % chance of being pathologic.

ACKNOWLEDGMENTS

The authors wish to express their appreciation to Dr. Earl Schubert and to Dr. Jack Curtis, formerly of the Cleveland Hearing and Speech Center, Cleveland, Ohio for their help in modifying the basic equipment to meet the needs of this study and their help in developing the technique used.

ZUSAMMENFASSUNG

Die hier beschriebene Technik, die DLF [illegible] Normalpersonen zu messen, gab Gruppenmittelwerte, die den Gruppenmittelwerten von Normalpersonen anderer Autoren entsprachen. Die Gruppenmittelwerte der DLF von Patienten mit M. Menière sind wesentlich höher als die Gruppenmittelwerte von Normalpersonen; die gleichen Beziehungen gelten für die Standardabweichungen in den beiden Gruppen. Die DLF von Patienten mit M. Menière zeigt umgekehrtes Verhalten zu der Reizintensität und hat in den tiefsten Frequenzen die grösste Abweichung vom Normalen. Tonunterscheidung (DL F) 100 und Streuung der Ergebnisse SD zeigt den Tiefstwert bei einer Frequenz von 4000 in der Menière-Gruppe verglichen mit einer Frequenz von 2000 in der Normalgruppe. Dies würde das obere Mittelstück und die Spitze der Cochlea bei M. Menière als mehr betroffen erscheinen lassen, wenn man die Tendenz zum Empfindlichkeitsverlust für tiefe Töne [illegible] nicht. Diese Untersuchungen der Frequenzunterscheidung, die in diesem Artikel beschrieben werden, sind keineswegs ein klinischer Test für M. Menière.

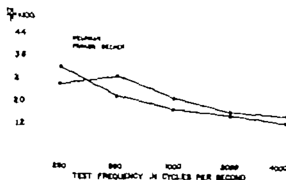


Fig 10

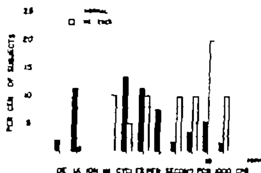


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EXPERIENCES IN THE TREATMENT OF VASOMOTOR RHINITIS

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Vasomotor rhinitis is the syndrome of a *number of* allergic and non allergic disturbances on the mucosa of the nose. Consequently before the treatment it is essential to find the real cause and remove or cure it. In our experience specific desensibilization is successful in monovalent sensibility and desensibilization with histamine in certain cases of physical allergy. The component part of our *treatment* in secondary infection must always be the curing of the sinuses, either by local treatment or conservative surgical treatment. In some cases the focus in the sinuses may be the source of bacterial allergy. Local treatment of the mucosa of the nose is the component part of our general treatment. Pure vasoconstrictors should *be avoided because of the increase reac*tion. Vasoconstrictors with an antihistamine principle and cortisone should be applied. In cases where our conservative treatment proves unsuccessful, dissection of the vidian nerve either unilaterally or bilaterally should be considered.

The etiology of vasomotor rhinitis being of many different types, the therapy cannot be uniform. We are of the opinion that every case of vasomotor rhinitis should be examined in detail both clinically and in the laboratory in order to be able to apply the appropriate therapy. The component parts of these examinations are the smear of the nose on eosinophyles, an X ray picture of *paranasal sinuses, allergic* tests, and, according to the history other laboratory and clinical examinations. The testing of eosinophyl in the smear of the nose should be performed several times bilaterally. In our experience, eosinophylia may appear even in non-allergic groups, as a component part of a parasympathicomimetic reaction, but if it is found strongly expressed in addition to the presence of eosinophylia in the blood, it is more frequently a symptom of allergic reactions. Regarding the intradermal tests on the *inhalants allergens and the treatment* by desensibilization in allergic vasomotor rhinitis, we cannot give a final and definite opinion. The reasons for this indecision are the following observation. Very often we noticed that, in the course of several intradermal tests, we obtained a different reaction not only according to quantity but also to *various allergens. In the course of the treatment* we sometimes had evident improvements in the nose although the intradermal reactions remained the same or were even increased. This is why we believe *that in* the evaluation of cutane tests it is necessary to take into consideration

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historical data and the degree of general nonspecific hypersensibility of the patient, which can play an important role in polyvalent sensibility During the last two years, since we started performing tests and desensibilization in vasomotor rhinitis, 381 patients have been tested, out of which 176 reacted negatively on inhalation allergens Of 205 patients reacting positively we had fewer cases of univalent and more of polyvalent sensitivity on the first four allergens, as shown in the table.

	Patients		Patients
House dust	157	Grass pollen	11
Animal hair	41	Tree pollen	33
Feathers	77	Moulds	25
Linen *of herbal origin*	88	Bacterial vaccine	44
Linen *of animal origin*	32	Monilia albicans	9
		Tobacco	19

On the basis of our experiences to date with specific desensibilization we offer the following conclusions about this therapy

1 The results are better in monovalent than in polyvalent sensitivity

2 The therapeut result does not always depend on the strength of the cutane reaction

3 We had the best results in the treatment with house dust and pollen

4 The objective finding in the nose does not correspond to the subjective changes In an unchanged objective status we have found the normalization of the subjective troubles or the opposite. The cutane tests need not change with the improvement of both subjective and objective signs

A great problem in vasomotor rhinitis is physical allergy It is our opinion that such a state does not actually represent an antigen anticorp allergic reaction, but that it is a repercussion of an exaggerated reflectory reaction in the sense of viscero-visceral reflexes whose basis is a neuro-endocrino imbalance In cases where histamine reaction was very pronounced we applied histamine desensibilization in very small doses over a period of 4 to 6 months and with a certain number of patients we noticed visible improvement Such improvements were present especially with those patients who had in addition a recurrent oedemata in the face and nose region.

Antihistaminics produce better results in acute allergic cases when the quantity of histamine in the shock organ is greater The antagonistic effect of antihistaminics is most pronounced on the smooth muscles, a little less pronounced on the reaction of histamine on the blood circulation and hardly visible on the secretion of mucous glands We came to the conclusion that various kinds of antihistaminics with the same patient can sometimes have a different effect.

The nose and paranasal sinuses are in fact a close whole and there are not any vasomotor reactions on the mucosa of the nose without the same

kind of reactions on the mucosa of the sinuses. Moreover the looser structure of the mucosa of the sinuses makes it possible for the oedemata on the mucosa of the sinuses to be more pronounced. *Where such conditions last* for a long time the blockade of the lymph vessels is possible especially if closing of the ostia of the sinuses appears, which then makes the creation of a secondary infection possible.

In our clinical material we found that nonallergic vasomotor rhinitis is *seldom found* without this secondary infection of the paranasal sinuses, especially of the maxillary sinuses. Consequently when this fact has been neglected in the therapy of *vasomotor rhinitis*, there might be created the focus, which not only supports vasomotor reactions of the mucosa of the upper respiratory tracts, but can also become *a potential source of bacterial* allergy.

In a number of patients we obtained satisfactory effects with conservative therapy by applying antibiotics, cortisone and proteolytic enzymes locally on the mucosa of the sinuses. When satisfactory results are not obtained with this therapy the surgical conservative treatment is undertaken. The surgical treatment on allergic and hyperergic areas always represents a potential deterioration of clinical symptoms. That is why such a procedure must be minimal and as much as possible atraumatic, avoiding the removal of the *mucosa of the sinuses and creating* favourable conditions for drainage and aerisation of the sinuses.

In vasomotor rhinitis *the operation of the septum is often performed un*necessarily. Only in those cases where even after vasoconstriction of the nasal mucosa, the conductability of the nose has not been established may we think that the anatomic factor of the deviated septum places a certain rol in the conductivity and the irregularity should be corrected. However in such cases we must also be conservative and remove only that part which causes obstruction.

The use of vasoconstrictors on the mucosa in vasomotor rhinitis, owing t parasympathomimetic reaction very often, after a shorte or longer period of time leads to the opposite reaction, i.e. to vasodilatation and the deterioration f the symptoms of the obstruction of the nose. In order to remo e this effect it is necessary to apply vasoconstrictors with antihistaminics and cortisone. Very often the question has been put as to how long this local therapy should be pplied. In ur *opinion results cannot be* expected from a short treatment but the therapy must be performed for a longer time. This combination *does n t do any harm* to the mucosa and fa ours biochemical balance in the mucosa of the nose, which i very important in such hronic *cases. This established balance* makes possible an early stoppage f vasomotor attacks, especially in non-allergic cases, in which we can *som times see that* neurovegetativ disturbances are spontaneously lo t.

We hav had *very good* experiences with 10 or 15 injections of calcium pplied strictly intramuscularly. It effect is also based on the establish-

ment of biochemical balance in the tissue, the strengthening of the cells membrane and the sympathic influence However we are aware of the fact that sometimes even with all these means, we are not able to effect a cure because it is very difficult from a wide syndroma to evaluate the real cause In such cases we can recommend the dissection of the vidian nerve i e the removal of the parasympathicomimetic reaction of the mucosa Although this method was inaugurated 4 years ago up to now we have operated only 6 cases This number is small because in most cases we attain success with conservative treatment with medicaments and secondly the patients dislike such operative procedures in vasomotor rhinitis. Last time we pointed out that after such an operation unilaterally the symptoms are often lost bilaterally We had an opportunity to follow a woman patient who had a relapse after two years, but only on the side where the dissection of the vidian nerve had not been performed This example speaks in favour of the possibility of a blockade of the parasympathic nerve by the dissection of the vidian nerve in vasomotor rhinitis Finally we should like to point out that a uniform therapy is not possible where there are syndromes of many diseases. Once again we wish to emphasize that, through anamnestic and clinical findings, the real cause must be found and removed Vasomotor rhinitis is still a rhinologic problem which is often the consequence of many pathophysiologic conditions of the organism and their repercussion on the mucosa of the nose and the upper respiratory tract

ZUSAMMENFASSUNG

Rhinitis vasomotoria ist ein Syndrom allergischer und nichtallergischer Störungen auf der Schleimhaut der Nase Infolgedessen ist es wichtig vor jeder Therapie den richtigen Grund zu ermitteln um ihn entfernen oder heilen zu können Nach unserer Erfahrung ist die spezifische Desensibilisation bei monovalenter Empfindlichkeit erfolgreich und unspezifische Desensibilisation mit Histamin in einigen Fällen physischer Allergie Ein wesentlicher Bestandteil unserer Therapie bei sekundärer Infektion muss immer die Heilung der Paranasalhöhlen sein sei es mittels lokaler Therapie oder durch konservative chirurgische Eingriffe In einigen Fällen kann diese Infektion eine Quelle bakterieller Allergie sein. Eine lokale Therapie der Nasenschleimhaut ist ein Bestandteil unserer allgemeinen Therapie. Reine Vasokonstriktoren mussen wegen inverser Reaktion vermieden werden statt dessen sollten Vasokonstriktoren mit antihistaminischem Prinzip und Cortison angewendet werden In Fällen wo sich unsere konservative Therapie erfolglos zeigt kommt eine Durchtrennung des Nervus vidianus, sei es einseitig oder beiderseitig, in Betracht

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COEXISTING VIRAL (RESPIRATORY SYNCYTIAL) AND BACTERIAL (PNEUMOCOCCUS) OTITIS MEDIA IN CHILDREN

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The occurrence of respiratory syncytial virus and bacteria in otitis media during RS virus infection was studied at a nursery. Middle ear aspirates were cultured for isolation of viruses and bacteria. Antibody responses to the isolated agents were followed. Otitis media was established in 11 of the 13 infected children. RS virus and *Diplococcus pneumoniae* type XIV were isolated from the middle ear exudates of 5 children. Both agents were simultaneously present in the exudates of 3 children. RS virus and *Diplococcus pneumoniae* were each isolated from one child. It was not possible to judge from the appearance of the ear drum or from the condition of the exudate the kind of agent present. The etiologic relationship between the isolated agents and the observed infection is discussed as well as the value of prophylactic antibiotic treatment.

Otitis media has been found to be common in respiratory syncytial (RS) virus infections (Reilly *et al.*, 1961; Kapikian *et al.*, 1961; Tóth *et al.* 1965; Berglund *et al.* 1965 *a*, 1966 *a*, *b*, 1967 *a*, *b*). By direct inoculation of middle ear exudates into cell cultures, Berglund and co-workers (Berglund *et al.*, 1966 *a*, *b*, 1967 *a*, *b*) were able to detect the RS virus in middle ear exudates from infants suffering from acute respiratory infection caused by this agent. In addition to this agent a bacterium (*Haemophilus influenzae*) was cultured from the exudate of one patient (Berglund *et al.* 1967 *a*). Because 20 of the 28 subjects studied by Berglund *et al.* had been under treatment with antibiotics at the time of the ear drum puncture, a coexisting bacterial infection could not with certainty be ruled out by negative bacterial cultures in these cases. In the present study additional information was sought on the role of bacteria in the aetiology of otitis media occurring during an RS virus epidemic at a nursery. It was possible to examine the children from the very beginning of their illness and to follow the development of middle ear infection in patients receiving no antibiotic treatment.

This report describes isolation of viruses (RS and adenoviruses) and/or bacterium (*Diplococcus pneumoniae*) from throat swab specimens and middle ear exudates of children with respiratory tract infection accompanying otitis media.

MATERIAL AND METHODS

The study was carried out in the spring of 1967 during an epidemic of respiratory infection at a nursery unit taking care of 13 children, whose age distribution was as follows

<3 mo	1
3– 5 mo	2
6–12 mo	5
12–36 mo	5

The conditions prevailing at the nursery have been reported by Berglund & Mantyjärvi (1966)

Specimens from the throats were taken with swabs and specimens of middle ear exudates by the puncture aspiration technique for viral and bacterial cultures. The techniques are described elsewhere (Lahikainen 1953 Berglund *et al.*, 1966 *a b*) Repeated otological examinations were performed during the course of the illness.

The preparation of cell cultures and the techniques of inoculating and handling these cultures have been reported previously (Berglund *et al* 1966 *a b* Berglund & Mantyjarvi 1966 Mäntyjarvi 1966) Identifications of RS virus and adenoviruses were carried out by the methods described by Berglund & Stråhlmann (1967) and Berglund & Mäntyjärvi (1966) respectively Bacteria were identified as described by Grönroos *et al* (1964)

Serum specimens were taken for antibody determinations in the acute phase of the illness and on several occasions later the last specimen after 2–6 weeks. The serum specimens were examined for complement fixing (CF) antibodies using the prototype Randall strain of RS virus as antigen and for neutralizing (N) antibodies using one of the isolated strains as antigen as described by Berglund *et al* (1967 c) The sera were also examined for CF antibodies to adenoviruses and haemagglutination inhibition (HI) tests were performed with adenovirus types 1 2 and 5 Antipneumolysin titres were kindly determined by Dr Costa Tunevall M D Sjukvårdsstyrelsens bakteriologiska centrallaboratorium Stockholm to whom we extend our sincere thanks

RESULTS

The first case (No 7) of the epidemic of respiratory infection occurred on February 5th and the second (No 13) on February 10th Two children (Nos. 1 and 8) became ill 3 days and three (Nos. 6 11 and 12) 4 days after the second child On February 16th four cases (Nos 2 3 4 and 5) and on the 28th two additional cases (Nos. 9 and 10) were observed According to the clinical signs, the illness in question resembled a respiratory syncytial virus infection This was confirmed by isolation of RS virus from throat specimens. Bronchitis without otitis was established clinically in only two

TABLE 1 *Isolation of viral and bacterial agents from throat and middle ear exudate specimens and antibody responses to various agents during an epidemic of acute respiratory infection in children at a nursery unit*

( ) Fourfold rise; RS = respiratory syncytial virus; AD = adenovirus; Pn = Diplococcus pneumoniae; unilateral; = bilateral; CF = complement fixing antibodies; \ = neutralizing antibodies; HI = haemagglutination inhibition, AP = antipneumolysin; — = no signs of otitis were observed.

Case no.	Age (months)	Clinical diagnosis	Isolation of infectious agent: Throat	Isolation of infectious agent: Ear	Significant rise of antibody titres: RS	Significant rise of antibody titres: Adeno	Significant rise of antibody titres: Pn
1	10	Bronchitis	RS AD2 Pn	RS Pn	(CF) \	CF + HI by AD5	
2	24	Inf. ac. resp.	RS	RS Pn[b]	CF + \		AP
3	8	Bronchiolitis	RS	RS P	(\)		
4	6	Pneumonia	RS	RS[b] Pn	CF + \		AP
5	24	Bronchitis	RS	RS[b]	CF + \		AP
6	9	Inf. ac. resp.	RS AD2 Pn	RS Pn	CF + \	CF (HI by AD2)	
7	11	Bronchiolitis	RS		CF + \		
8	5	Bronchopneum.	RS	Pn	(CF)		AP
9	4	Bronchiolitis	RS AD2 Pn		(CF) + (\)	CF HI by AD2	
10	1	Bronchitis	RS		—		
11	30	Bronchitis	RS		CF + \		AP
12	12	Bronchitis	RS		CF + \		
13	24	Bronchitis	RS		CF + \		

cases. Six children were found to have bronchitis, one pneumonia, one bronchopneumonia and three bronchiolitis. The features of RS virus infections observed during the earlier outbreak by Berglund *et al.*—nasal discharge, cough, involvement of the lower respiratory tract, and accompanying middle ear infection— were the main manifestations of the illness also during this epidemic.

Four of the children (Nos. 5, 7, 8 and 10) were transferred to three different hospitals. These children could not be followed to the same extent in all respects as the other children; this concerned especially case No. 7.

Four cases (Nos. 2, 3, 11 and 13) were known to have had an RS virus infection during an outbreak 15 months earlier (Berglund & Mäntyjärvi, 1968).

Otitis media was established in 11 of the 13 diseased children. Signs of middle ear inflammation appeared before the second day after the onset of the disease in six cases, before the third day in two, and before the fourth day in one case. The two remaining cases showed signs of middle ear infection on the 10th and 14th day after the onset of the illness. The signs disappeared within 6 to 24 days, in seven cases within two weeks or less.

The RS virus was isolated from throat swabs taken from every infant during the first two days of the disease (Tables 1 and 2). Only in three

TABLE 2. *Clinical features of otitis media viral and bacterial isolates*

Date of onset is underlined.

Case	Date	Ear drum	Appearance	Amount of aspirate	Quality of aspirate
1	13.2.				
10 mo	15.2.	1.dx.	Dull, reddened rigid, bulging	+ +	Turbid mucous
		1.sin.	Dull, reddened rigid, bulging	+ +	Turbid, mucous
	22.2.	1.a.	Thickened, dull, pale rigid	+	Sticky mucous
	28.2.	1.a.	Normal		
2	16.2.				
24 mo	17.2.	1.dx.	Reddened refl. visible, slightly rigid	+	Turbid, mucous
		1.sin.	Dull, refl poorly visible slightly rigid	+	Turbid, mucous
	22.2.	1.a.	Thickened, dull, reddened, rigid	+ + +	Turbid mucous
	28.2.	1.a.	Thickened, dull I jected, rigid	+ + +	Sticky mucous
	6.3.	1.a.	Normal		
3	16.2.				
6 mo	17.2.	1.a.	Thickened, dull rigid	+	Muco s
	20.2.	1.a.	Dull, reddened, rigid bulging	+ + +	Sticky mucous
	24.2.	1.a.	Thickened dull, slightly reddened, rigid	+ +	Mucous
	28.	1.dx.	Thi kened dull, rigid bulging	+ + +	Turbid, mucous
		1.sin.	Dull	+	
	6.3.	1.dx.	Normal		
		1.sin.	Slightly injected	±	
	14.3.				
	30.3.				
4	16.2.				
6 mo	17.2.	1.dx.	Dull, slightly reddened rigid, bulging	+ +	Sticky mucous
		1.sin.	Dull, slightly reddened rigid, b lging	+ +	Sticky mucous
	20.2.	1.a.	Bulging	+ +	Sticky turb. mucous
	24.2.	1.dx.	Thick ned, dull rigid	+ + +	Mucous
		1.sin.	Thickened dull, rigid	+ + +	M cous
	28.2.	1.a.	Thickened, dull	−	
5	16.2.				
24 mo	17.2.	1.a.	Pale dull, rigid, bulging, small haem rrh.	+ + +	Sticky turbid mucopurulent
	22.2.	1.a.	Pale thicke ed slightly redd ed rig d, bulging	+ +	Stick turb. mucous
	28.2.	1.a.	Slightly injected	+ + +	Sticky turb. mucous
	6.3.	1.dx.	Dull, rigid	+ +	Sticky turb. mucous
		1.sin.	Radial I jected	+ +	Sticky turb mucous
	13.3.	1.a.	*Dull*	+ +	*Sticky* mucous
6	14.2.				
9 mo	17.2.	1.a.	Normal		
	20	1.dx.	Thickened, dull, slightly reddened	+	T rbid mucou

as well as antibody responses of infants with respiratory infection

NT not tested.

Nasal culture		Culture of throat specimens		Antibiotic treatment started	Serum antibody titres				
					RS		Adeno		Pn
Viral	Bact.	Viral	Bact.		CF	N	CF	HI	AP
		RS AD2	NT						
RS	—			15.2.	<4	<4	32	20 (AD5)	100
RS	Pn			(Penic.)					
—	—	AD2	Pn			8	32	20 (AD5)	100
					4	16	2.6	40 (AD5)	200
		RS	—						
RS	—				<4	<4	64		50
—	—								
—	Pn	—	—	22.2.		128	64		32
—	—	(inf.)	—	(Penic.)		128	32		140
					64	>128	64		00
—	—	RS	—		<4	<4	64		2.0
RS	Pn	RS	—	20.2.		<4			
	—	—	—	(Penic.)		<4	32		50
	—	—	—			4			
					<4	4	64		50
					<4	4			
	Pn	RS	—		<4	<4	16		70
RS	—								
RS	Pn	R	—	20.2		<4			
	—	RS	—	(Ampic.)					
RS	—								
					4	16	64		200
					8				
		R	—						
RS									
				17.2.	<4	<4	128		0
				(Penic.)					
	—	—	—						
		—	—			64			
	—	—	—			128			
					128	64	64		200
	—	—	—						
						64	128		
		RS AD2	NT						
RS	—	R	—	20.2.	4	<4	64	AD2 10	100
						<4			

Films stained by Gram method yielded Gram-positive ovale capsulate cocci. The serum antibody titres are given as reciprocals of the serum dilutions. For further abbreviations, see Table 1.

TABLE 2 (*Continued*)

Case	Date	Ear drum	Appearance	Amount of aspirate	Quality of aspirate
		1 sin	Dull slightly reddened	+	Turbid, mucous
	24.2.	1.a.	Thickened, dull, rigid	+ +	Turbid, mucous
	28.2.	1.a.	Thickened, dull	+	Sticky mucous
	3.3	1.a.	Thickened, dull	+	Mucous
	9.3.	1.dx.	Thickened, dull slightly reddened	+	Mucous
		1.sin.	Normal		
	13.3.	1.a.	Normal		
7	*5*				
11 mo	8.2.				
	9.2.	1.a.		+	
	22.2.	1 dx.	Thickened pale dull rigid	+	Fluid, mucous
	2.3	1 sin.	Thickened, pale dull	+	Fluid, mucous
	8.3.	1.a.	Thickened		
8	*13.2.*				
5 mo	14.2.				
	24.2.	1.a.	Thinn reddened, refl. visible rigid	+	Sticky mucous
	3.3.	1 dx.	Thinn, dull, rigid	+	Haemorrh., mucous
		1.sin.	Thinn dull	–	
	8.3.	1.a.	Normal		
	14.3.				
	22.3				
	6.4				
9	*28.2*				
4 mo	*1.3*	*1 dx.*	*Dull, slightly injected*	±	*Clear serous*
		1.sin.	Dull, slightly injected	+ +	Turbid, mucous
	6.3.	1.a.	Thickened dull, slightly reddened, rigid bulging	+ + +	Sticky purulent
	13.3	1 dx.	Skanty discharge		Mucous
		1 sin.	Thinn, slightly rigid radial injected	+ +	Mucous
	17.3.				
	20.3.	1.a.	Thicken d, dull rigid, injected	+	Mucous
	29.3.	1.a.	Normal		
	6.4.				
10	*28.—*				
1 mo	1.3.	1 dx	Dull, slightly redd ned rigid, b lgi g	+	Sticky turb. mucous
		1.sin	Dull, reddened	+ +	Sticky turb. mucous
	9.3.	1 dx.	Thickened, rigid	+	Sticky mucopurulent
		1 sin.	Normal		
	13.3.	1.a.	Normal		
	30.3.				
11	*14.2.*				
30 mo	15.2.				
	3.3.	1.a.	Thickened radial injected	+ +	Clear serous
	9.3.	1.a.	Normal		

Aspirate culture		Culture of throat specimens		Antibiotic treatment started	Serum antibody titres				
					RS		Adeno		Pn
Viral	Bact.	Viral	Bact.		CF	N	CF	HI	AP
—	Pn			(Penic.)					
—	—	RS	Pn			<4			
—	—	—	—			8	128		
—	—	—	—			16			
—	NT	AD2	—		32	8	>256	AD2 10	100
		RS	H. infl.	8.2.					
NT	Str. viridans			(Ampic.)	<4	<4	4		140
—	—					16	8		280
—	—								
					64	32	8		140
		RS	NT	13.2.	<4	<4	32		50
—	—	RS	—	(Penic.)		<4	32		200
—	Pn	—	—			<4	32		
					<4				
					4	<4			
					<4	<4	2.6		200
					<4	4	32		
—	NT	RS AD2	—	1.3.	<4	<4	<4	<10 (AD2)	
—	—			(Penic.					
				1 3.3.)					
—	—	AD2	Pn			4			
—	Prot. mir.	RS	—			<4			
—									
		RS AD2	NT	14.3.		<4	4	10 (AD2)	50
	—	—	—	(T. trac.)					
					4	4	4	10 (AD2)	36
					4	4	8	20 (AD2)	
	—	RS	—	1.3.	<4	32	8		280
—		—	—	(Terram.)					
						32	4		
					<4	32	8		70
		RS	NT						
—		—	—		4	4	64		100
				3.3.	64	64	32		0
				(Penic.)		64	32		200

TABLE 2 (*Continued*)

Case	Date	Ear drum	Appearance	Amount of aspirate	Quality of aspirate
12	*14 2.*				
12 mo	14 2.				
	2.3.				
13	*16 2.*				
24 mo	14 2.				
	2.3.				
	17.3				

cases was the RS virus found in throat swabs taken one week after the first successful isolation In the one case (No 9) in which RS virus was isolated from a throat swab taken on the 17th day after the onset of the illness, a relapse had occurred *Diplococcus pneumoniae type XIV* and adenovirus type 2 were also isolated from the throats of three infants (Nos. 1 6 and 9)

RS virus was isolated from the middle ear exudates of six children (Nos. 1–6) from 12 specimens in all RS virus without any accompanying agent was isolated bilaterally from one child (No 5) In three cases (Nos. 2, 4 and 6) in which RS virus was isolated from the middle ear exudates, the virus was simultaneously isolated from the throat specimens In the other cases it was isolated earlier from the throat specimens.

Diplococcus pneumoniae type XIV was established in middle ear exudates of six children (Nos 1–4 6 and 8) from 13 specimens in all RS virus and *Diplococcus pneumoniae type XIV* were both established in exudates aspirated from six ears (Nos 1 3 and 4) In two cases (Nos 4 and 6) the RS virus was isolated from the exudate from one ear while pneumococcus was isolated from the exudate aspirated from the other ear

Pneumococcus only was isolated unilaterally from the middle ear exudate of one child (No 8)

In case No 7 who first fell ill *Streptococcus viridans* was isolated from the exudate of the middle ear taken at the hospital *Proteus mirabilis* was isolated from the exudate of case No *9 It* was, however *not detected on* staining and hence its presence in the culture was most probably due to contamination

The middle ear exudate specimens obtained on three different occasions from one of the children were all positive for RS virus This was the only case in which pneumococcus was also isolated from specimens taken on the first repeated puncture four days after the first puncture Of the children known to have experienced a re infection, only one did not exhibit signs of otitis media

…parate culture		Culture of throat specimens		Antibiotic treatment started	Serum antibody titres				
					RS		Adeno		Pn
Viral	Bact	Viral	Bact.		CF	N	CF	HI	AP
		RS	NT		< 4	< 4	> 128		34
					64	64	64		50
		RS	NT		< 4	< 4	128		70
					16	> 12[illegible]	64		100
						64	128		100

It has thus been definitely demonstrated that both RS virus and bacteria can be present in middle ear exudates and hence have to be considered as aetiological factors in otitis media occurring during RS virus infections. As only one case of coexisting RS virus and bacterial otitis media has been reported previously the clinical features, viral and bacterial isolates, as well as the serum antibody responses of our cases are summarized in Table 2.

The signs of middle ear inflammation and the conditions of the exudates are listed in Table 3. Dullness, redness and bulging of the ear drum were the signs most often observed. It was not possible for the examiner to draw any conclusions from the appearance of the ear drum or from the condition of the exudate as to the kind of agent later isolated from the exudate. The signs seemed, however to be weaker in ears yielding RS virus only than in ears yielding both RS virus and pneumococci.

Continuous accumulation of exudate in the middle ear occurred in one infant (No.) with a cleft palate until the adenoids were extirpated. In this case the anatomical circumstances had influenced the course of the middle ear inflammation.

The RS virus infection was verified by a significant rise of CF and/or neutralizing antibody titres in 9 cases. The RS virus CF antibody titres of the acute serum phase were less than 4 in all cases and the neutralizing antibody titres were less than 4 in all but the one infant aged one month (No. 10) in whom the titre was 32. Eight children showed an 8-fold or greater rise in titre and six showed titres of 64 or higher. Only a two-fold rise in CF and/or neutralizing antibody titres occurred in three children, and no increase of antibodies to RS virus occurred in *one infant aged* 1 month.

Three of five children (Nos. 1, 4, 6, 8 and 9) found positive for adenovirus type 2 developed a 4 fold or greater rise of CF antibodies to adenoviruses. In only two cases (Nos. 6 and 9) was the rise of the HI antibodies

TABLE 2 (*Continued*)

Case	Date	Ear drum	Appearance	Amount of aspirate	Quality of aspirate
12	11 2.				
12 mo	14 2.				
	2.3.				
13	10 2.				
24 mo	14.2.				
	2.3.				
	17.3.				

cases was the RS virus found in throat swabs taken one week after the first successful isolation In the one case (No 9) in which RS virus was isolated from a throat swab taken on the 17th day after the onset of the illness, a relapse had occurred *Diplococcus pneumoniae type XIV* and adenovirus type 2 were also isolated from the throats of three infants (Nos. 1 6 and 9)

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Pneumococcus only was isolated unilaterally from the middle ear exudate of one child (No 8)

In case No 7 who first fell ill *Streptococcus viridans* was isolated from the exudate of the middle ear taken at the hospital *Proteus mirabilis* was isolated from the exudate of case No 9 It was, however not detected on staining and hence its presence in the culture was most probably due to contamination

The middle ear exudate specimens obtained on three different occasions from one of the children were all positive for RS virus. This was the only case in which pneumococcus was also isolated from specimens taken on the first repeated puncture four days after the first puncture Of the children known to have experienced a re-infection only one did not exhibit signs of otitis media.

negative for adenovirus in this study and the rise of HI antibodies for *adenovirus* type 5 in case No. 1.

Viruses and bacteria can obviously be simultaneously present in middle ear exudates. It cannot in all cases be postulated with certainty *to what* extent pneumococcus was also aetiologically *related* to the infection of the *lower respiratory* tract and which of the two agents was the primary cause of the respiratory illnesses. If we take into consideration the two children from whom pneumococcus was *not* isolated but in whom a significant rise in antipneumolysin titre occurred, *there* were ten children *in all* who *evidently* had contracted a pneumococcal infection in addition to the RS virus infection. The typical clinical finding of RS virus infection in these children indicates that the RS virus most likely was the primary agent and that pneumococcal superinfection had occurred. RS virus infection may *have promoted the spread of pneumococcus* among the children in the nursery and paved the way for pneumococcal superinfection. On the basis of our own results we do not definitely know in which order these agents invaded the middle ear but it seems that it could have happened simul*taneously in some of the children*.

The present study provides further evidence of the importance of taking specimens for the isolation of viruses at an early stage of the illness. Attempts to isolate RS virus from throat specimens obtained after the first *successful isolation* yielded *negative results when these specimens were* taken 10 days—in most cases 7 days—after the onset of the illness. RS virus could not be isolated from the middle ear exudates later than one week after the first positive puncture and only in one case from specimen *taken at repeated punctures*.

It is noteworthy that no pneumococci were isolated from children receiving antibiotics at the time of puncture and that no bacterial otitis media developed in two children (Nos. 3 and 10) who were treated with antibiotics *from the very onset of* the illness. Bacterial middle ear inflammation and most likely also other bacterial superinfections may be prevented by prophylactic treatment with antibiotics in RS virus infection. *The prophylactic antibiotic treatment may be of value in respiratory in*fections caused by RS virus, *especially during institutional RS virus out*break and in cases where the infant is exceptionally exposed to contacts.

Only one infant aged 1 month showed no increase in antibodies to RS virus. This is in accordance with the fact that the antibody response to RS virus infection is poor in very young infants. The low antibody titres to RS virus found in case No. 1 may be explained by a too short sampling interval of only two weeks because of the discharge of the infant from the nursery. *According to previous* experience significant rises in RS virus antibody titres do not occur in infants less than 3 months *old before 3 to 4* weeks have elapsed from the onset of the illness (Berglund *et al.* 1965 *a*).

The low rise in HI antibody response to adenovirus type 5 infection which afflicted infant No. 1 early in January and the absence of antibody

TABLE 3 *Signs of otitis media in and conditions of exudates from ears positive for RS and/or pneumococcus*

	RS	RS + Pn	Pn
Ear drum			
Thin			1
Thickened	2		4
Pale	2		
Dull	3	5	7
Reddened	2	5	4
Haemorrhagic	2		
Bulging	2	6	1
Rigid	4	0	7
Exudate			
Mucous	4	6	7
Mucopurulent	2		
Turbid	4	4	5
Sticky	2	4	1
Sanguinic			1
No of ears	6	6	7

demonstrated with the type isolated from the throat whereas in the remaining three cases HI antibodies to a different type or no HI antibodies were established

A significant rise in antipneumolysin titre occurred in five children. Pneumococci were isolated from middle ear exudates from three of these children whereas they were not isolated from any specimen from the two remaining children No rise was observed in 5 further children harbouring pneumococci

DISCUSSION

Two concomitant agents, RS virus and *Diplococcus pneumoniae type XIV* had evidently been the causal agents in the epidemic of respiratory illness studied. RS virus is known to spread easily among infants at nurseries with high resultant infection rates (Sterner *et al.*, 1966) In the present study all infants at the nursery unit were involved. It is also known that of pneumococcal infections those caused by *Diplococcus pneumoniae* of *type XIV* are the most prevalent among infants, that the healthy carrier rate of this type is very low and that institutional spread of this type among infants does occur (Finland 1942 Smillie & Jewett 1942) In addition to the two causal agents found, adenovirus type 2 may have contributed to the infection in three cases of the present series. From the beginning of January 1967 adenoviruses 1 and 5 had repeatedly been isolated from several infants showing slight signs of respiratory infection This well explains the significant rises in adenovirus CF antibody titres in children found

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response to adenovirus type 2 isolated from this infant in the middle of February may be ascribed to retarded antibody production.

As to antipneumolysins, it is known that the antibody response to pneumococcal infection is of low order in young infants (Tunevall 1953) The youngest infant of this series developed no antibodies to pneumolysin Four of five children in which low antibody response to viral agents were observed failed to produce antibodies to pneumolysin.

Whether RS virus is also associated with the so-called sterile otitis frequently found in older age groups (Gronroos *et al* 1964) remains an open question. The coexistence of viral and bacterial infection of the middle ear necessitates further virological and bacteriological investigations to elucidate the interactions of both types of agents in middle ear inflammation

ZUSAMMENFASSUNG

Das Auftreten von RS-Virus (respiratory syncytial) und Pneumokokken in Mittelohrentzündung wurde während einer RS-Virusepidemie in einem Kleinkinderheim an 13 Kindern untersucht Zwecks Isolation von Viren und Bakterien erfolgten Viruszüchtungen aus Mittelohraspiraten Die den isolierten Krankheitserregern entsprechenden Antikörper wurden beobachtet Eine Mittelohrentzündung konnte bei 11 der untersuchten 13 Kleinkinder festgestellt werden Sowohl der RS-Virus als *Diplococcus pneumoniae Typ XIV* wurde aus den Mittelohrexsudaten von 5 Kindern isoliert Gleichzeitig waren beide Krankheitserreger in den Exsudaten dreier Kinder vorhanden Bei einem Kind wurde der RS-Virus und desgleichen bei einem Kind *Diplococcus pneumoniae* isoliert Weder aus dem Aussehen des Trommelfells noch aus der Beschaffenheit des Exsudates konnten hinsichtlich der Art des Krankheitserregers irgendwelche Schlüsse gezogen werden Zur Diskussion standen sowohl die äthiologischen Beziehungen zwischen den isolierten Krankheitserregern und der beobachteten Infektion einerseits und anderseits die Bedeutung prophylaktischer Behandlung mit Antibiotika.

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exist, as these may indicate central initiation and control of the frequency pattern. In this case the frequency and the amplitude must be regarded as expressions not only of the peripheral stimulus but also of the condition of those areas of the brain stem which are engaged in initiating the fast phases.

A decrease in wakefulness will abolish the fast phase and turn the eyes in the direction of the slow component (Nathanson & Bergman, 1958). *With returning wakefulness the fast phase* will reappear probably first giving a low frequency. As a consequence an increase in wakefulness may cause an increase in frequency with a corresponding decrease in amplitude. As smoking has been found to increase the alertness, as judged by EEG (Yamamoto & Domino, 1964) a simultaneous change of the nystagmus pattern might be expected. With this background studies of the nystagmus pattern before and after smoking were carried out. In the present work the amplitude and the frequency of the nystagmus beats, the velocity of the slow and fast components, as well as the deviation of the eyes, were compared before and after smoking.

METHODS AND MATERIAL

Twenty-one healthy subjects, ten females and eleven males varying in age from 20 to 33 years, were examined. They were classified, according to their smoking habits, into occasional smokers (0–4 cig./day $n = 7$) moderate smokers (5–10 cig./day $n = 7$) and heavy smokers (11–20 cig./day $n = 7$).

Performance of the Test

The experiments were performed in darkness with the test subject sitting in a rotating device which could be exposed to an angular acceleration of 120°/sec 1.8 sec. The head was free to move in any direction. The subject was instructed to keep the eyes open during the whole test. Each subject was rotated for one minute at three different times: before, immediately after and fifteen minutes after smoking.

For the smoking part of the test the subject *was allowed to smoke a* non-filter cigarette (John Silver Swedish Tobacco Company) for three minutes. One deep inhalation of smoke was made every fifteen seconds. Immediately after the last inhalation the rotation was started. The test subject had not been allowed to smoke during the previous two hours. After a time-interval varying between 4 to 21 days the test was repeated on each subject.

Before the start of rotation every test subject was calibrated with respect to horizontal eye and head movements of twenty five degrees from the mid-point. The mid-position of the eyes was checked before and after rotation.

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EFFECT OF CIGARETTE SMOKING ON THE VESTIBULAR NYSTAGMUS PATTERN

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Cigarette smoking was shown to give rise to obvious changes of the vestibular nystagmus pattern and these changes were ascribed to central influences. It was demonstrated that the fast phase affected the nystagmus pattern by changing its velocity but above all by changing the time for its interruption of the slow phase. Early interruptions thus increased the frequency and decreased the amplitude. The qualities initiated in the vestibular receptor, the speed of the slow component and the deviations of the eyes in the direction of the fast component, were not significantly changed. Heavy smokers were found to have less changes in the nystagmus pattern by smoking than moderate smokers.

A vestibular nystagmus reaction is made up of a slow and a fast component. The angular velocity of the slow component is found to express very faithfully variations in the vestibular stimulus (Henriksson, 1956) while that of the fast component can be varied by changes within the central nervous system (CNS) (McCabe 1965).

The frequency and the amplitude have also been used for evaluation of the nystagmus pattern. Their relation to the vestibular stimulus and the velocity of the slow component is however somewhat complex. Torok (1948) has found that the frequency and Mittermaier (1955) that the amplitude to some extent will reflect the vestibular stimulus. However as the product of frequency and amplitude equals more closely the speed of the slow component than either of the two (Ohm 1939) neither of the factors will be as good a measure of the peripheral stimulus as the speed of the slow component itself.

A variation in frequency at constant vestibular stimulus and constant speed of slow component cannot be brought about without a simultaneous change in amplitude. Such a variation can only be caused by changes of the time for interruptions of the slow phases by the centrally controlled fast phases. Early interruptions must then give an increase of the frequency and a decrease of the amplitude while late interruptions may give the opposite pattern. It is therefore of interest to find out if such variations

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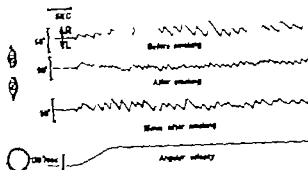
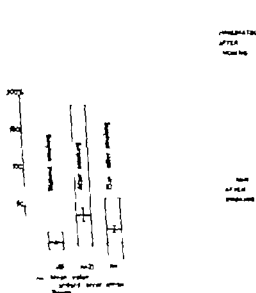


Fig. 1 Horizontal ey movement l lockwise rotation i darkness with pen eyes.



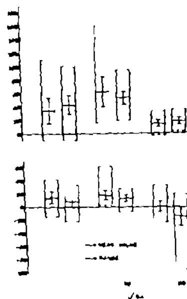


Fig. 2 Fig. 3.

Fig. 2 Average difference of ystagm freq cncles (beat per ten seconds) i per nt (Betwe lues obt ined fter t rot tions three minutes part without moki g; B bet een l es btained before nd immediately fter smoking; C bet een al es obtained befor nd fifteen minutes fter smoking.

Fig. 3 Mea increment of ystagm frequency (beats per ten seconds after sm king in pe cent of mea frequency without smoking, at tw different occ ions of rot tion and for three groups ith different moking habits. A First occasion; B, second oc sion

tude w seen The peed of the slow component and the deviation of the yes in the direction of th fast component were not affected, while the peed f the f st component showed a marked decrease. The rotations caused negligible ngular deviation of the head before as well as after moking Fifteen minutes after moking the nystagmus had not fully regained it pre- moking pattern Th values at this time however did not diff r significantly from those before sm king

Recordings

The movements and the position of the eyes were recorded by means of a DC-technique described by Lundgren Tibbling & Henriksson (1967) This technique allows registration of the horizontal nystagmus movements and the degree of deviation of the eyes. The movements and positions of the head were recorded by means of a potentiometer on the head of the test subject and the angular velocity of the rotation device by means of a tech nique based on a frequency rate principle All recordings were made on a 4-channel ink writer (Mingograf 81 Elema Sweden)

Analysis of the Tracings

The nystagmus tracings were analyzed at 2 4 10 18 and 30 seconds after the onset of the acceleration with respect to frequency amplitude speed of fast and slow components, and position of the eyes The frequency was determined by counting the number and the fractions of the nystagmus beats per second at the different times and also during the first ten seconds immediately after the start of the rotation To get a representative expres sion of the amplitude this was calculated at each time as the average amplitude of three or more consecutive amplitudes. The speeds of the fast and slow components were calculated from the DC-tracings as degrees per second

The deviation of the eyes was measured at the end of the fast component and calculated as the angular displacement from the mid position of the eyes For these calculations the drift potential apparently caused by the tobacco smoking, had to be considered Thus when the position of the eyes was measured after rotation and a drift potential exceeding five degrees per minute was found the calculated value was corrected with the assump- tion of a continuous drift

Methods for Statistical Analysis

At each of the three occasions of rotation and for each quality at 2 4 10 18 and 30 seconds after the start of rotation the mean values with their standard deviations and standard error of means were calculated The comparisons between the qualities before and after smoking were statistically evaluated by use of the "student s" *t* test

RESULTS

The nystagmus pattern showed very pronounced changes after smoking as can be seen in Fig. 1 The analyzed qualities are summarized in Table 1 The frequency was the quality which showed the greatest change This change was most significant during the fourth and tenth seconds after the start of the rotation that took place immediately after smoking To- gether with the increase in frequency a corresponding decrease in ampli

Table 1 (cont.)

Sec. after start of rotation	Amplitude	Frequency	Speed of slow comp.	Speed of fast comp.	Deviation
10	12.7±1.0	2.3±0.1	35±10	216±10	10.8±2.5
	(5.9 23.6)	(1.5 3.2)	(10–68)	(148–360)	(–8 35)
	—	—	—	—	—
15	11.1±0.9	2.1±0.1	26±3	190±11	11.4±2.3
	(4.0 20.5)	(1.0 3.1)	(4 48)	(70–206)	(–8 32)
	—	—	—	—	—
20	8.2±0.9	1.3±0.1	13±2	161±12	9.3±2.4
	(0.0 15.0)	(0.0–2.5)	(0 30)	(70 260)	(–10–20)
	—	—	—	—	—

To get a more simple method of measuring the frequency this was determined during the first ten seconds after start of rotation. In Fig. 2 the mean increment of the frequency immediately after and fifteen minutes after smoking is given in per cent of the mean frequency before smoking. Although there were great variations in the individual values, the mean increment from before to immediately after smoking was statistically highly significant ($p > 0.001$) whereas there was no statistical difference between the values obtained before and fifteen minutes after smoking. On comparison very slight changes were found in the nystagmus pattern when ten subjects were rotated without smoking at three consecutive occasions with intervals of three minutes (Fig. 3 A). Repetition of the entire test showed good reproducibility (Table 2).

When the twenty-one test subjects were divided into three different groups according to their smoking habits, their nystagmus patterns after smoking were influenced in the same manner but to a varying extent (Table 2). Immediately after smoking, those who could be classified as occasional smokers showed a moderate increase in frequency of nystagmus beats (average 37%) while moderate smokers showed the largest (average 45%) and heavy smokers the least (average 16%) (Fig. 3). Fifteen minutes after smoking, the frequencies in the occasional and moderate smokers had not returned to pre-smoking values, but the differences were not significant. On one occasion (Fig. 3 A) the mean frequency of the heavy smoker group was equal to the pre-smoking frequency while on another occasion (Fig. 3 B) it was even lower than the mean pre-smoking value. These differences, however, were not significant.

DISCUSSION

Nylling & Kruse (1961) have reported that spontaneous vertical nystagmus appears after smoking. In the present investigation of vestibular induced nystagmus we have recorded conspicuous changes in frequency and amplitude after smoking.

TABLE 1 *Effect of smoking on the per rotatory nystagmus pattern in 21 subjects*

Mean values of amplitude (degrees) frequency (beats/sec) speed of slow and fast component (degrees/sec) and eye deviation (degrees) are given with standard error of the mean and ranges at 2, 4 10 18 and 30 seconds after start of angular acceleration (120 /sec/1.8 sec) p-values refer to comparison between values found before and immediately after or fifteen minutes after smoking
Horizontal bars represent p-values > 0.05

Sec. after start of rotation	Amplitude	Frequency	Speed of slow comp	Speed of fast comp.	Deviation
		Before smoking			
2	13.3±0.9 (6.6 – 21.6)	3.0±0.2 (1.0 – 4.5)	52±3 (34 – 80)	193±10 (98 – 183)	13.1±1.8 (–4 – 30)
4	13.1±0.8 (5.2 – 20.0)	2.7±0.1 (1.7 – 3.6)	49±3 (32 – 80)	204±11 (75 – 285)	7.1±1.8 (–8 – 20)
10	12.7±1.0 (6.0 – 23.8)	2.4±0.1 (0.8 – 3.1)	39±3 (18 – 70)	202±12 (128 – 335)	3.0±1.3 (–8 – 14)
18	11.5±0.9 (4.6 – 19.5)	1.9±0.1 (0.9 – 2.5)	27±3 (8 – 60)	170±9 (75 – 250)	4.1±1.6 (–6 – 20)
30	8.5±1.0 (0.0 – 17.6)	1.3±0.1 (0.0 – 2.0)	16±2 (4 – 40)	155±10 (49 245)	1.6±2.7 (–20 – 28)
		Immediately after smoking			
2	10.8±1.0 (2.0 – 24.5) —	3.8±0.3 (1.9 – 7.6) $p < 0.02$	61±4 (28 – 92) —	163±14 (38 – 320) —	9.0±2.7 (–16 – 30) —
4	10.4±0.9 (4.4 – 18.0) $p < 0.05$	3.7±0.3 (1.9 – 6.5) $p < 0.005$	48±4 (24 – 80) —	167±12 (65 – 260) $p < 0.05$	5.7±2.3 (–24 – 22) —
10	9.9±1.1 (4.6 – 26.4) —	3.0±0.1 (2.0 – 4.0) p 0.001	35±3 (17 – 64) —	157±11 (73 – 255) $p < 0.01$	4.7±2.4 (–20 – 22) —
18	8.0±0.8 (3.0 – 17.2) $p < 0.01$	2.3±0.1 (1.2 – 3.2) $p < 0.02$	22±3 (9 – 43) —	139±10 (0 220) —	3.4±2.6 (–16 – 36) —
30	5.9±0.8 (0.0 16.0) $p < 0.05$	1.2±0.2 (0.0 – 2.4) —	10±2 (0 – 26) —	136±8 (80 – 185) —	6.1±2.3 (–10 – 42) —
		15 minutes after smoking			
2	14.9±0.9 (7.2 – 23.5) —	3.1±0.2 (2.2 – 5.0) —	60±4 (24 – 82) —	231±9 (1 6 – 336) —	17.3±2.2 (3 40) —
4	14.0±1.1 (5.6 – 25.5) —	3.0±0.1 (2.0 – 4.5) —	52±4 (19 – 86) —	229±11 (148 360) —	11.5±2.1 (–3 – 34) —

Table 1 (cont.)

Sec. after start of rotation	Amplitude	Frequency	Speed of slow comp.	Speed of fast comp.	Deviation
10	12.7±1.0 (3.9 23.4) —	2.5±0.1 (1.5 3.2) —	35±16 (10–64) —	210±10 (118 300) —	10.8±2.[illegible] (–8 3) —
15	11.1±0.9 (6.0–20.5) —	2.1±0.1 (1.0–3.1) —	20±3 (4 48) —	190±11 (70 296) —	11.1±2.3 (5 32) —
30	8.2±0.9 (0.0 15.0) —	1.3±0.1 (0.0 2.5) —	13±2 (0 30) —	161±12 (0 280) —	9.3±2.1 (10 29) —

To get a more simple method of measuring the frequency this was determined during the first ten seconds after start of rotation. In Fig. 2 the mean increment of the frequency immediately after and fifteen minutes after smoking is given in per cent of the mean frequency before smoking. Although there were great variations in the individual values, the mean increment from before to immediately after smoking was statistically highly significant ($p > 0.001$) whereas there was no statistical difference between the values obtained before and fifteen minutes after smoking. On comparison very slight changes were found in the nystagmus pattern when ten subjects were rotated without smoking at three consecutive occasions with intervals of three minutes (Fig. 3 A). Repetition of the entire test showed good reproducibility (Table 2).

When the twenty-one test subjects were divided into three different groups according to their smoking habits, their nystagmus patterns after smoking were influenced in the same manner but to a varying extent (Table 2). Immediately after smoking, those who could be classified as occasional smokers showed a moderate increase in frequency of nystagmus beats (average 37%), while moderate smokers showed the largest (average 45) and heavy smokers the least (average 10%) (Fig. 2). Fifteen minutes after smoking, the frequencies in the occasional and moderate smokers had not returned to pre-smoking values, but the differences were not significant. On one occasion (Fig. 3 A) the mean frequency of the heavy smoker group was equal to the pre-smoking frequency while on another occasion (Fig. 3 B) it was even lower than the mean pre-smoking value. These differences, however, were not significant.

DISCUSSION

Neveling & Kruse (1961) have reported that spontaneous vertical nystagmus appears after smoking. In the present investigation of vestibular induced nystagmus we have recorded conspicuous changes in frequency and amplitude after smoking.

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Horizontal bars represent *p*-values > 0 05

Sec after start of rotation	Amplitude	Frequency	Speed of slow comp.	Speed of fast comp.	Deviation
		Before smoking			
2	13.3±0.9 (6.6–21 6)	3.0±0.2 (1 6–4.5)	52±3 (34–80)	195±10 (98–183)	13.1±1.8 (–4–30)
4	13.1±0.8 (5.2–20 0)	2.7±0 1 (1 7–3 6)	49±3 (32–80)	204±11 (75–285)	1±1.8 (–8–20)
10	12.7±1 0 (6.0–23.8)	2.4±0.1 (0.8–3.1)	39±3 (18– 0)	202±12 (128–335)	3.0±1.3 (–8–14)
18	11.5±0.9 (4 6–19.5)	1 9±0.1 (0.9–2.5)	27±3 (8–60)	1 0±9 (5–250)	4 1±1 6 (–6–20)
30	8.5±1 0 (0 0–17 6)	1.3±0.1 (0 0–2.0)	16±2 (4–40)	165±10 (49–245)	1 6±2.7 (–20–28)
		Immediately after smoking			
2	10.8±1 0 (2.0–24.5) —	3.8±0.3 (1 9–7 6) p < 0.02	61±4 (28–92) —	103±14 (38–320) —	9.0±2.7 (–16–30) —
4	10 4±0.9 (4 4–18.0) p < 0.05	3 7±0 3 (1 9–6.5) p < 0.005	48±4 (24–80) —	187±12 (03–200) p < 0 05	5.7±2.3 (–24–22) —
10	9 9±1 1 (1 6–26.4) —	3.0±0.1 (2.0–4 0) p < 0.001	35±3 (17–64) —	157±11 (75–235) p < 0 01	4.7±2.4 (–20–22) —
18	8 0±0.8 (3.0–17 2) p < 0 01	2.3±0.1 (1.2–3 2) p < 0 02	22±3 (9–43) —	139±10 (0 220) —	3 4±2.6 (–16–36) —
30	5 9±0.8 (0 0–16.0) p < 0 03	1 2±0 2 (0 0– 4) —	10±2 (0 26) —	130+8 (60 185) —	6.1±2.3 (–10–42) —
		15 minutes after smoking			
2	14 9±0 9 (7.2–23 5) —	3.1±0.2 (2.2–5 0) —	60±4 (24–82) —	231±9 (1 0 336) —	1 3±2.2 (3 10) —
4	14.0±1 1 (5.6–25.5) —	3 0±0 1 (2. –4.5) —	52±4 (19 86) —	229±11 (148–360) —	11 ±2.1 (–3–34) —

not only with respect to its velocity but also in respect to its ability to interrupt the slow phase. Thus the frequency and the amplitude must depend not only on variations in the vestibular stimulus, but also on the activity of the parts of the brain stem which are engaged in initiating the fast phases.

It is possible that the changes obtained in the frequency–amplitude pattern may be due to a decrease in wakefulness causing a deviation of the eyes in the direction of the slow component. Such a deviation could be expected to diminish the amplitude at least at extreme deviation. However as smoking has been found to change the EEG-pattern (Yamamoto & Domino, 1964) in a way indicating an increase of alertness, a deviation in the direction of the slow component cannot be expected. Further, our technique allows us to measure the position of the eyes during the whole test and no such deviation was found. Therefore an explanation for the changes in the nystagmus pattern must be looked for in other mechanisms. A decrease of the velocity of the fast phase would tend to lower the frequency instead of increasing it. In spite of this, our results show an enhancement of the frequency after smoking. Therefore, variation in the time interval for the interruption of the slow component by the fast phase must be the main source for the changes in the nystagmus pattern.

From our results we conclude that it is possible to influence selectively the centrally induced fast phase without affecting the slow one. Thus, while the speed of slow component and the deviation in the direction of the fast phase are expressions of the peripheral sensitivity the frequency pattern can be used as a tool for studying the conditions within the central nervous system.

The pharmacological background for the changes found in the nystagmus pattern is at the present time difficult to explain. Probably the inhaled nicotine may in some way cause variations in the blood supply to certain brain areas which, as a consequence, will influence the nystagmus. The changes of the nystagmus pattern can also be attributed to a direct effect of nicotine on the nervous cells or the central synapses. However a combination of the mechanisms mentioned cannot be excluded. A further possibility might be that the concentration of carboxy-hemoglobin in the blood after smoking tends to decrease the oxygen supply to the brain tissue. Carbon monoxide, however, is eliminated rather slowly (about 15 of % per hour by normal ventilation) while the changes of the nystagmus pattern described had reverted to normal in about half an hour.

The occasional smokers, as compared to the moderate smokers, showed only a moderate increase in frequency per ten seconds after smoking. This may be related to the fact that occasional smokers do not inhale the smoke from the cigarette deeply enough and therefore absorb less nicotine through the lungs (Larson, 1960).

The fact that there was only a moderate increase in frequency in the heavy smokers may be explained by a central habituation effect of smok-

TABLE 2. *Effect of smoking on the per rotatory nystagmus patterns obtained from three groups of subjects with different smoking habits*

Mean value of frequency with standard error of mean and ranges is given before, immediately and fifteen minutes after smoking. *p*-values refer to comparison between values found before and immediately after or fifteen minutes after smoking. Horizontal bars represent *p*-values > 0.05

		Frequency (beats/10 sec.)		
Cig./day	Occasion	Before smoking	Immediately after smoking	15 min after smoking
0–4	I	25.3 ± 1.8 (19 – 34)	32.9 ± 3.0 (22 – 46) —	28.1 ± 1.4 (24 – 35) —
$n = 7$	II	27.3 ± 1.5 (23 – 33)	39.3 ± 4.7 (21 – 60) p < 0.05	29.4 ± 2.7 (18 – 40) —
5–10	I	25.3 ± 1.5 (20 – 33)	39.9 ± 3.5 (29 – 57) p < 0.03	29.4 ± 1.0 (26 – 33) —
$n =$	II	28.1 ± 1.2 (24 – 32)	43.1 ± 3.6 (32 – 62) p < 0.03	31.4 ± 1.6 (27 – 40) —
11–20	I	28.3 ± 1.3 (24 – 34)	32.3 ± 1.8 (24 – 39) —	28.6 + 2.5 (21 – 38) —
$n = 7$	II	30.0 ± 1.9 (23 – 39)	35.4 ± 2.3 (2[illegible] – 43) —	23.8 + 2.9 (22 – 41) —

The analysis of the influence of smoking on the vestibular nystagmus pattern shows that the two qualities reflecting the peripheral stimulus, the speed of the slow component and the deviation in the direction of the fast component, are quite unaffected. On the other hand the speed of the fast component, which has been proven to be generated by the CNS (McCabe 1965), decreases markedly. Such a decrease was also found by de Kleyn & Versteegh (1922) in induced caloric nystagmus in rabbits, when toxic doses of nicotine were administered. In the present study, in spite of a constant vestibular stimulus in different tests, and in spite of identical vestibular responses judged from the speed of the slow component, the frequency increased and the amplitude decreased immediately after smoking. This can only be brought about by the fast phase interrupting the slow one more frequently. This indicates that the fast phase is changed by smoking

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TELEMETRY SYSTEM FOR NYSTAGMUS RECORDING

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ENG is the most satisfactory method for nystagmus recording and for scientific purposes it has been developed to the point where it is a very reliable tool. Simplified commercial types of ENG apparatus are available and permit recordings of vestibular examination so that all relevant parameters can be registrated objectively. The advent of special types of semiconductors has permitted the construction of telemetry systems for ENG. One of the advantages of using radio transmission is, *inter alia*, that vestibulo-ocular as well as vestibulo-spinal reactions may be investigated simultaneously.

Högyes (1881) in his studies on the connection of the labyrinth with the ocular muscle nuclei, was the first to describe a method by which ocular movements could be recorded via a pneumatic system on a revolving smoked drum. Berlin (1891) was the first to record nystagmus in man. The principle of his method was to place on the cornea an ivory shell connected with a brush hair which recorded the ocular movements on a watch glass. Buys (1900) and Ohm (1914) also used mechanical principles, but utilized the movement transmitted to the upper eyelid due to the difference in the curvature of the cornea and sclera on movements of the eyeball.

A number of photographic methods were described, *inter alia* by Dohlman (1925) one of the few to obtain good results thereby. Kristensen & Zilstorff Pedersen (1953) used an ophthalmograph for cinematographic registration of the eye movements. However these methods were not clinically applicable. In 1951 Torok *et al* introduced the photoelectric method (PENG) based upon the difference in the reflection of light from the cornea and sclera. This method has not, however, come into major use in daily clinical work.

Electronystagmography (ENG) was first described by Schott in 1922. ENG is based on the cornea retinal potential difference and has become a clinically applicable method. Great progress has been made by ENG, *inter alia* in the research of Aschan *et al* (1956), Henriksson (1956) and Montandon & Rusbach (1956). To-day it is an indispensable clinical aid, especially in examining patients with weak vestibular disturbances.

In recent years transistorization of the ENG apparatus has led to the development of miniature, high quality amplifiers and new types of re-

ing As a consequence this may indicate that heavy smokers obtain less stimulation by their smoking than do the moderate smokers.

For a proper understanding of the variations in the nystagmus pattern obtained after smoking in subjects with different smoking habits, a more extended investigation is in progress.

ZUSAMMENFASSUNG

Das vestibulare Nystagmusmuster zeigte deutliche Veränderungen nach Zigarettenrauchen Diese Veränderungen könnten den zentralen Einflüssen zugeschrieben werden Es hat sich gezeigt, dass die schnelle Phase die langsame Phase beeinflusst hat dadurch dass die Schnelligkeit der schnellen Phase und insbesondere der Abbruch der langsamen Phase von der schnellen verändert wurden. Frühzeitigere Abbrüche ergaben eine erhöhte Frequenz und eine gesenkte Amplitude Die im vestibularen Rezeptor initiierten Qualitäten — die Schnelligkeit der langsamen Komponente und die Augendeviationen in der Richtung der schnellen Phase — waren nicht signifikant verändert Die obengenannten Qualitäten wurden verwertet, um den Mechanismus der zentralen induzierten schnellen Phase zu erklären Starke Raucher demonstrierten im Muster des vestibularen Nystagmus weniger Veränderungen beim Rauchen als mässige Raucher

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TELEMETRY SYSTEM FOR NYSTAGMUS RECORDING

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ENG is the most satisfactory method for nystagmus recording and f scientific purposes it has been developed to the point where it is a very reliable tool. Simplified comm rcial type of ENG pparatus are available and permit recordings of estibular examin tion, so that all relevant parameters can be registrated bjecti ely. The advent of special types of semiconductors has permitted the co struction of telemetry systems for ENG. One of the d antages of using radio transmission is, *inter alia*, that vestibulo-ocular as well s vestibulo-spinal reactions may be investigated simultaneously.

Högyes (1881) in his studies on the connection of the labyrinth with the ocular muscle nuclei, was the first to describe a method by which ocular movements could be recorded via a pneumatic system on a revolving smoked drum. Berlin (1891) was the first to record nystagmus in man. The principle of his method was to place on the cornea an ivory shell con nected with a brush hair which recorded the ocular movements on a watch glass. Buys (1909) and Ohm (1914) also used mechanical principles, but utilized the movement transmitted to the upper eyelid due to the difference in the curvature of the cornea and sclera on movements of the eyeball.

A number of photographic methods were described, *inter alia* by Dohl man (1925), one of the few to obtain good results thereby. Kristensen & Zilstorff Pedersen (1953) used an ophthalmograph for cinematographic registration of the eye movements. However these methods were not linically applicable. In 1951 Torok *et al* introduced the photoelectric method (PENG) based upon the difference in the reflection of light from the cornea and sclera. This method has not, however come into major use in daily clinical work.

Electronystagmography (ENG) was first described by Schott in 1922. ENG is based on the cornea-retinal potential difference and has become a clinically applicable method. Great progress has been made by ENG, *inter lia* in the research of Aschan *et al* (1956), Henriksson (1956) and M n landon & Rushbach (1956). To-day it is an indispensable clinical aid, especially in examining patients with weak estibular disturbances.

In recent years transistorization f the ENG apparatus has led to the de elopment of miniature high quality amplifiers and new types of re

ing As a consequence this may indicate that heavy smokers obtain less stimulation by their smoking than do the moderate smokers.

For a proper understanding of the variations in the nystagmus pattern obtained after smoking in subjects with different smoking habits, a more extended investigation is in progress

ZUSAMMENFASSUNG

Das vestibulare Nystagmusmuster zeigte deutliche Veränderungen nach Zigarettenrauchen Diese Veränderungen könnten den zentralen Einflüssen zugeschrieben werden Es hat sich gezeigt dass die schnelle Phase die langsame Phase beeinflusst hat dadurch dass die Schnelligkeit der schnellen Phase und insbesondere der Abbruch der langsamen Phase von der schnellen verändert wurden Frühzeitigere Abbrüche ergaben eine erhöhte Frequenz und eine gesenkte Amplitude Die im vestibularen Rezeptor initiierten Qualitäten — die Schnelligkeit der langsamen Komponente und die Augendeviationen in der Richtung der schnellen Phase — waren nicht signifikant verändert. Die obengenannten Qualitäten wurden verwertet um den Mechanismus der zentralen induzierten schnellen Phase zu erklären Starke Raucher demonstrierten im Muster des vestibularen Nystagmus weniger Veränderungen beim Rauchen als mässige Raucher

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FIG. 2. Perso connected with FM transmitter

type E35P002. In order to ascertain the tuning accuracy an indicator instrument was connected to the Foster Seeley discriminator of the IF amplifier The frequency stability was controlled by means of an AFC (automatic frequency control) circuit. The detected ENG signal was recovered directly from the output terminals of the discriminator

Recording Equipment

The signals were recorded both on a mingograph 24 and a Tektronix 502 Oscilloscope With the mingograph in position D (DC-amplifier) the telemetry system used has a time constant of 2 sec. In position A (AC-amplifier) of 1 sec.

RESULTS

Fig. 4 gives some transmitted curves. The transmitting distance was 25 m Curve A shows the appearance of a number of calibration pulses Curves B and C sh w caloric and postrotatory nystagmus re pecti ely The time constant is 1 sec Curve D is from a patient with a post-concussion syndrome showing spontaneous nystagmus present only in th dark or behind losed eyelids. The tim constant was 2 sec

COMMENTS

It has been the purpose of th present study to d monstrate the possibility of using telemetry systems for transmitting ENG signals. The

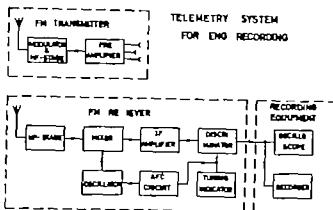


Fig. 1 Diagram showing telemetry equipment

cording techniques One possibility is the transmission of the signals via radiotelemetry The purpose of the present paper has been to evaluate such a method in practical use

Apparatus and Method

The potentials to be recorded in the ENG are usually in the range 50–100 microvolts and thus put great demands upon the internal noise of the amplification system the time constant of the amplifier and the common mode rejection of the circuit These demands can be met by using transistors with particulary low noise and the employment of differential coupled amplifiers

Furthermore it is important that the frequency range of the transmitter is wide enough to transfer the signal without undue distorsion and that the output of the transmitter is suitable with the natural limitation, that it must not disturb other systems Fig 1 gives a block diagram of the telemetry equipment developed in our department

Transmitter

The ENG potentials from the patient are amplified in a differential amplifier with the following specifications (Fryer & Deboo, 1965) Input impedance 10 megaohms gain 60 dB common mode rejection 80 dB The amplified ENG signals are used to modulate the HF stage of the FM transmitter The modulation signals cause small changes in the emitter current and the collector emitter voltage This changes the collector emitter capacity and thus gives the desired frequency swing (Roy & Hart 1966) The oscillator frequency may be adjusted between 88–100 MHz by means of a variable capacitor in the tank circuit of the HF stage The FM transmitter has a maximum range of 100 m

FM Receiver

The receiver (Fig 3) was constructed from commercial components and consisted of a Torotor FM Tuner type FE 31AA and Torotor IF amplifier

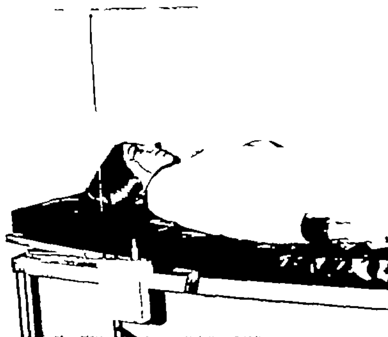


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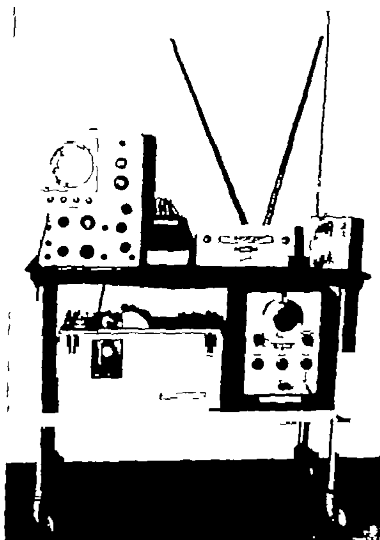


Fig. 3 FM recei e with recording equipment

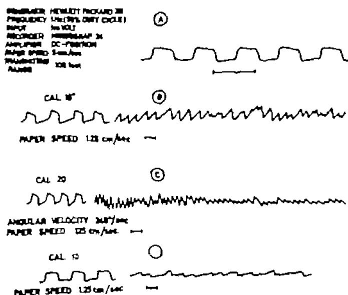


Fig. 4 Nyst gmu curves traced by mean f t l metry A Calibrati n curv B lorie nystagmus C, postrotat ry nystagm D po t neou n st gmu

quality of the curves is of such a standard that the different parameters such as maximum eyespeed, frequency and duration, can be calculated in an entirely adequate way.

There are several advantages in using telemetry in ENG. The study itself and the tracing of the curves need not take place in the same room. This may be practical in examining debilitated or dizzy patients, as they can remain in their beds. Telemetry can be done directly from patients on the operating table during operations on, e.g., the stapes or during ultrasonic treatment of the vestibular organ.

The portable FM transmitter permits the simultaneous investigation of several vestibular reactions, such as nystagmus on the one hand and pointing deviation, blindfold walking, Romberg's test or the stepping test (Pettersen, 1965) on the other.

Finally telemetry may facilitate recordings when using rotation chairs for vestibular tests, as it obviates the disadvantages of the slipring contacts. It is too early to say whether telemetry is going to gain ground within ENG in the same way as within ECG, but from a technical point of view there is nothing to prevent this.

ZUSAMMENFASSUNG

Die Elektronystagmographie (ENG) ist bis jetzt die beste und verbreitetste aller Methoden zur Nystagmusregistrierung — und die die zu den besten Ergebnissen geführt hat. Die kommerziell hergestellte ENG-Apparatur ist vereinfacht worden, so dass sie für Vestibularisuntersuchungen verwendet werden kann sowie die Parameter mit genügender Qualität wiedergibt, woran man interessiert ist. Die Herstellung spezieller Transistortypen hat die Konstruktion von telemetrischen System für ENG ermöglicht. Der Vorteil der Telemetrie gegenüber der konventionellen Nystagmusregistrierung ist u.a., dass sowohl die vestibulo-okulären als die vestibulo-spinalen Reaktionen gleichzeitig untersucht werden können.

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Acta Oto Laryngologica 50 years

It is common knowledge that the creation of *Acta Oto-Laryngologica* is to be ascribed entirely to Gunnar Holmgren. Chiefly with a view to strengthening co-operation between oto-rhino-laryngologists in Scandinavia Holmgren started *Oto-Laryngologiska Meddelanden* in 1912 and *Nordisk Tidskrift för Oto Rhino-Laryngologi* in 1916 It soon became evident that these journals were of great importance for furthering scientific research in Scandinavia. Difficulties did, however arise in getting the original articles reviewed in the international literature. Holmgren therefore decided, in 1918 to present a new journal, *Acta Oto-Laryngologica* with papers written in English, French, and German. Subsequently in collaboration with colleagues in numerous countries, Acta Oto-Laryngologica developed into a leading specialist journal. Holmgren emphasized at an early stage that an essential feature was, precisely collaboration with many countries abroad a fact that has been amply confirmed during the whole life of the journal.


Gunnar Holmgren


Paul Frenckner

In addition to the regular issues of Acta Oto Laryngologica the numerous supplements have proved to give our readers fundamental surveys and monographs in current fields of research. Hitherto 250 supplements have been published Many of them are theses for the doctorate of medicine from the Scandinavian countries and have made outstanding contributions to questions of topical interest.

It is the hope of the Editorial Board of Acta Oto-Laryngologica that we will in the future be able to continue in the same spirit, and with the same success, as our founder Gunnar Holmgren and his successor Paul Frenckner

C A Hamberger
Editor in Chief

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AUDIOMETRIC IDENTIFICATION OF NORMAL HEARING CARRIERS OF GENES FOR DEAFNESS

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As most carriers of genes for recessive deafness do not display hearing impairment to a greater extent than average it is impossible to identify suspected gene carriers by ordinary audiometry. In the study reported here more advanced test methods, namely Békésy audiometry and the stapedius reflex test, have been applied in an attempt to detect any subclinical peculiarities in the hearing. The material consisted of a group of 30 parental pairs with normal hearing and a strong indication of genetic deafness. They had 74 children, 47 of them with severe genetic hearing impairment or total deafness. On comparison with a control group, two peculiarities were found in the hereditary series, namely small but distinct dips in the middle frequency range of the hearing threshold and abnormally high thresholds for the acoustically elicited stapedius reflex.

The observations are discussed against the background of earlier genetic and histologic findings.

Deafness in children is not a unitary clinical concept, rather the term covers a group of distinct pathologic conditions whose causes are to be sought among a number of factors and agents and where the auditory system may have been damaged at widely separated sites and at quite different ages—even *in utero*.

Deafness is divided into two main groups according to whether it is hereditary or acquired. Pre-, peri- and postnatal sub-groups are recognized, according to the time of onset. Congenital hearing defects may be either hereditary or acquired and either pre- or perinatal.

It has hitherto been extremely difficult to identify the cause of childhood deafness in the individual case. The classification is made on the basis of the medico-audiologic examination and the history, and especially the family history. ("Look at the family rather than at the individual", said Alexander Graham Bell in 1891.) The forthcoming information relating to deaf relatives must be weighed against any potentially detrimental exogenous factors that might be considered to have a bearing on the child's hearing before, during or after birth, and against the objective findings of the examination. In some cases a hereditary background is so obvious that the hearing defect may be ascribed an endogenous cause. Often, how-

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C A Hamberger
Editor in Chief

Hereditary deafness satisfies the four postulated conditions for inborn errors of metabolism

Provided that the tests are subtle enough, many hereditary diseases may be disclosed in their symptomfree carriers by minor deviations from the normal. If a person is a heterozygote for a complaint he has one normal and one mutant gene. Since each *gene is responsible for* the formation of its own protein, which is often an enzyme, in the case of a changed genetic structure the mutant gene will either have prevented the formation of this particular enzyme or it will have given rise to an abnormal enzyme.

There are, however, no biochemical tests by which it is possible to detect any abnormal activity in enzymes responsible for the development and function of the auditory system. For this reason it has not been possible to class hereditary deafness as an inborn error of metabolism, but this does *not rule out the possibility that it belongs to this group. It means* only that our knowledge of the involvement of these enzymes in the biologic process is still too limited to be able to ascertain the biochemical basis of these defects.

There remains the possibility of demonstrating the effect of any enzymatic defects on the hearing organ in gene carriers by audiometric studies. Such attempts have been made in order to detect heterozygotes among the parents of children considered to have a genetic hearing impairment (Wildervanck, 1937, Fraser, 1964). From an examination of 15 normal hearing parental pairs with their 32 children with recessive deafness Wildervanck inferred that it was impossible by ordinary audiometry to *identify these parents as heterozygotes*. "The conclusion of my *entire investigation* is that normal hearing parents of children with deafness are not detectable as heterozygotes." Nor could Fraser find any significant hearing impairment in heterozygotes in sex linked recessive deafness. It may thus be assumed that any hearing defects in the heterozygotes are subclinical and that to obtain a solution of the problem more refined methods than have been used so far must be applied.

The present study constitutes an attempt by advanced audiometric techniques to identify carriers of mutant recessive and intermediate genes of deafness and thus to obtain a better impression of the mode of inheritance of this condition than has hitherto been possible.

METHODS

In earlier attempts to identify heterozygotes of deafness by audiometric method, reliance has been placed solely on octave audiometry. This method is sensitive enough to disclose clinical defects, but this was not the case in the supposed heterozygotes in whom any defects would have been subclinical. However, no previous study has been made of how these respond to more advanced or sensitive tests. Such a subtle test is provided by the Békésy audiometry where, by the continuous recording of the hearing

ever no cause of the hearing impairment *can be found* and the case must then *be assigned* to the "unknown group but there is every reason to suppose that in this group too the hearing defect will usually have a genetic origin

In short, the consensus is that the hereditary group comprises about one half of all the child cases of severe hearing impairment. In the hereditary group the recessive subgroup is by far the largest Opinions diverge, how ever on the frequency of recessive hearing impairments in hereditary deaf ness Arnvig (1953) gives more than 90 per cent, with about 5 per cent dominant while Fraser (1964) puts the figure at more than 70 per cent with 25 per cent dominant and a small number of sex linked

On the mode of inheritance of deafness numerous theories have been proposed (Lundborg 1912, 1920 Albrecht 1922 Dahlberg, 1931 Ham merschlag, 1932, 1934 Johnsen, 1952) The dominant form has been the subject of many studies over years (Stephens & Dolowitz, 1949 van Eg mond, 1954 Mártensson, 1960 Wildervanck 1962 Huizing *et al* 1966) and here the detection of carriers presents no problem, just as is the case for other dominant genetic defects.

These theories have not so far however yielded any explanation of the mode of inheritance in the commonest type of hearing defect, the recessive sensory neural hearing impairment Many families have been described in which both parents were recessively deaf but whose children all had normal hearing (Hammerschlag, 1934 Lehmann 1950) It must therefore be as sumed that there are several if not many different genes situated in dif ferent loci and that in the homozygotic form they give rise to deafness It is thus justified to speak of the recessive forms of deafness. Opinions differ on the number of loci for such abnormal genes which can give rise to recessive deafness Chung *et al* (1959) who carried out an analysis of a series collected by Stevenson & Cheeseman (1956) assessed their number at 36 while Sank (1963) put it considerably higher "at least 45"

Of the causal connection between defective genes and hereditary deafness we know still less than about the mode of inheritance In our search for an approach to the investigation of these causes interest has been focused on a type of disease where an enzyme defect is the underlying cause, namely inborn errors of metabolism

This term was coined as early as 1908 by Sir Archibald Garrod the English physician for a pathologic entity comprising the 4 diseases albinism alkaptonuria cystinuria and pentosuria They had certain common traits (1) They could be demonstrated in the first days of life (2) they tended to occur frequently in certain families in a large number of cases (3) they were fairly benign and compatible with a normal length of life (4) they often appeared in the offspring of consanguineous marriages. Garrod's prophecy that the underlying cause of these diseases would prove to be an enzyme defect has proved correct From the original number of 4 the inborn errors have now increased to more than a hundred (Hsia 1966)

be masked by or confused with, exogenous defects. For instance those parental pairs were excluded a member of which showed anamnestically and audiometrically characteristic impairment of obviously exogenous causation (conductive impai ment, defects through n lse drugs, etc.) to an extent that interfered with the evaluation of the result. The only kind of threshold elevation of possible e o-genous origin to be accepted was the hearing impairment at higher frequencies associated with age—presbyacusis—which is well known and extensively docu mented. This exception was necessary bec use the parent gro p was hetero-geneous with respect to age. The parents hearing threshold was therefore in this respect assessed in relation to the mean for the corresponding age and sex groups of the Wisconsin State Fair Hearing Survey (WSFHS, Glorig et al 1957) after ppropriate correction for difference in calibration of audiometers. For the difference in audiometric methods (Békésy a. octave audiometry) however no correction was made.

(3) Both marriage partners should be available and willing to undergo examination.

For practical reasons the study was limited to parents consulting the Depart ment of Audiology Karolinska Hospital for their children deafness. To obtain some measure of randomnes in the selection such parental pairs resident in a certain geograph cal area were supplem nted with an equal number of pairs chosen in order of registration at the Department, irrespectiv f their place of residence

After the selection on the basis of the above criteria there remained in the geographic group 15 families resident in the area served by the Manilla School for the Deaf These constituted all the recorded subjects in the area who satisfied the above criteria. The 15 families had 44 children (28 boys, 16 girls) 25 of whom were deaf (18 boys, 7 girls) The other data are presented in Table 4

The chronologic group consisted of 15 families from the clientele who consulted the Department during 1964–65 and who likewise satisfied the above criteria. These families had 30 children (14 girls, 16 boys) 22 of whom were deaf (13 boys, 9 girls) Other details are given in Table 4

The hereditary series of parents thus consisted altogether of 30 families w th 74 children, 47 of whom were deaf (totally o profoundly hard of hearing) The age of th parents at the time of the study ranged from 21 to 71 years for th men (mean 42.8) and 22 to 65 years for the women (mean 35.9)

The presence f a genetic background is confirmed by the fact that n les than 14 of the families had 2 or more children with impaired hear ing In 12 of the families there was, moreo er information on hearing d fects in other relatives, though not with a d minant mode of inheritance

Of the 47 childr n 32 were totally deaf and 15 had severe hearing im-pairment, but with measurable residual hearing. In 10 of these 15 the hearing impairment had progressed during an observation period of more than 10 years. Such progress has been found to be a distinctive feature of

threshold it is possible to observe even small peculiarities or deviations. Another possibility is to subject the auditory system to a certain load by a test well above the threshold with the object of detecting defects that are not manifested in the threshold test This possibility is provided by determination of the threshold for the stapedius reflex a method that also has the advantage of objectivity

All subjects in the present study were submitted to a carefully ear examination and relevant medical history were recorded The hearing tests were performed in a sound proof chamber by an experienced operator The hearing thresholds (125–8000 Hz) were recorded with the Grason–Stadler Békésy audiometer type E 800 calibrated in accordance with the ISO standard (R 389 1964)

The stapedius reflex was recorded by the technique described by Klockhoff & Anderson (1959) and Klockhoff (1961) The acoustic stimulus was delivered by an octave tone audiometer calibrated in accordance with ISO standard R 389 and satisfying the requirement of ICE Recommendation no 177 (1965) The threshold for the stapedius reflex was established for the test tone octaves 125–4000 Hz and half octaves 1500 and 3000 Hz. The determinations were made in 5-dB steps and the maximum available output for 500–4000 Hz was 120 dB and for 250 Hz, 100 dB (hearing level) The reflex measurements enable the presence also of minor conductive impairments to be excluded with a high level of reliability (Klockhoff & Anderson 1959 Klockhoff 1961) an important fact for the evaluation of the test results

MATERIAL

Hereditary series

The hereditary series consisted of parental pairs with at least one child with deafness that was judged to be endogenous Since the object of the study was to detect recessive and intermediate carriers, all families with a dominant mode of inheritance were excluded Unlike the dominant carrier the recessive and intermediate ones are known to be free from symptoms and for this reason only those presumed gene carriers with subjectively normal hearing were included in the series

The following criteria were applied in selecting the parental pairs

(1) The children's deafness should be classified as "probably endogenous" This means that the case history and the examination disclosed no exogenous cause of the defect and that (i) the child had siblings with defective hearing of likewise unknown cause, and/or (ii) that the examination revealed an apparently high incidence of "inexplicable hearing impairments of an early onset in the parents relations

(2) The parents hearing should be subjectively normal

As has been pointed out earlier the recessive and intermediate heterozygotes are assumed to display no *clinical signs or symptoms. For any* subclinical endogenous peculiarities to be detectable by means of hearing tests they should not

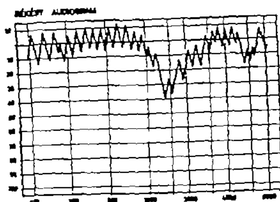


Fig. 1. Example of dip in hearing threshold recorded by Békésy-audiometry. Note that its position is such that the significant characteristic of the dip might be missed in routine octa[ve a]udiometry (family No. 23, mother, left ear).

parents also proved to have audiometrically normal hearing or in some cases, extremely slight defects. To assess the possibility of there being an exogenous or endogenous cause of these small irregularities in the hearing threshold curves the authors considered it appropriate in the analysis to di[v]ide them into two frequency ranges

(i) 3000–6000 Hz which has been found to be the most [v]ulnerable to exogenous agents and where presbyacusis sets in

(ii) 250–3000 Hz which is extremely resistant to exogenous agents and where impairments caused by them are almost invariably noticed only when the hearing in the upper frequency range is severely impaired. This destruction pattern is also characteristic of presbyacusis: the high frequency range is invariably sever[e]ly impaired before the lower range is affected.

In order to find whether the hearing threshold in the range 3000–6000 Hz might be regarded as average a comparison was made with the corresponding age and sex groups from the Wisconsin State Fair Hearing Survey (Glorig *et al.* 1957). It was f[o]und that for 56 of the 60 parents (93 per cent) the hearing lay within the semi-interquartile range: for 42 it was distinctly better than the median. For only 4 of the fathers did the threshold fall outside the 7[5] percentile at at least 2 frequencies, still without being high enough to make the subject aware of the impairment.

In th[e] frequency range 250–3000 Hz, too, the parent series as a whole showed no significant [e]le[va]tion of the hearing threshold. Howe[v]er some [o]f th[e] subject[s] recorded well defined elevations in the otherwise normal hearing threshold although small, these "dips" were quite distinct and ea[s]y t[o] distinguish in the Békésy recording. They varied in depth and [e]xtent. To be classed as significant it was stipulated that they should be [a]t least 20 dB (hearing level), extend o[v]er at least one octave and be not

endogenous hearing defects (Barr & Wedenberg 1965) The markedly recessive nature of the series is confirmed by the severe hearing impairment of the probands in relation to the subjectively normal hearing of the parents, and the fact that no less than 3 of the marriages were between cousins.

Control groups

To be able to decide whether a certain peculiarity in otherwise normal hearing might be considered as an endogenous stigma it is necessary to know its degree and incidence in an average population In this respect large scale studies on normal subjects are of little help since small individual variations are bound to disappear with the form of presentation generally used The presence of peculiarities in the hearing threshold was therefore examined by Békésy audiometry in a control series The selection followed the same general lines as for the hereditary series—that is to say—there should be subjective normal hearing while obviously exogenous perceptive and conductive impairment that might interfere with the observations were excluded Békésy audiometric examinations were carried out on 60 women and 73 men aged 21–24 years

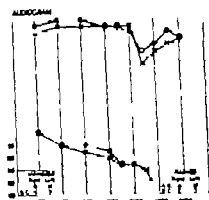
This material was supplemented with an anlysis of the results of an octave-audiometric screening study of 10 778 14 year-old school children (5623 boys, 5155 girls) from Stockholm schools. Its purpose was to examine the hearing of a group before it was significantly exposed to exogenous strain Although the audiometric procedure used here was considerably less sensitive than the Békésy technique for detecting minor peculiarities in the hearing threshold—and hence less significant as test—this analysis was nonetheless regarded valuable as it shows the incidence of the features of interest in a young still intact" group as determined with the most common form of audiometry

The subjects used in the study of individual deviations in the reflex threshold must fulfil extremely high requirements with respect to the hearing threshold This sharpening of the requirements was regarded necessary to exclude even slight signs of exogenous influence which are known first to appear as minor deviations in the threshold of hearing usually in the upper frequency range To be acceptable for the reflex test the subject was required to have not only perfect middle-ear condition but also a Békésy hearing threshold better than 15 dB in the range 250–4000 Hz, and better than 20 dB in the ranges 125–250 and 4000–8000 Hz Fifty of the women and 50 of the men meeting these requirements provided the control group for the stapedius reflex test

RESULTS

Hearing threshold in the hereditary series

A prerequisite for the hereditary loaded parental pairs to be accepted in this study was subjectively normal hearing The analysis shows that the


Fig. 2.

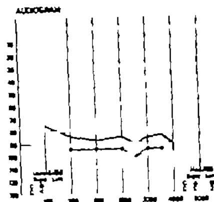

Fig. 3

Fig. 2. Example of abnormally high reflex thresholds (dash-dotted). Values within shaded area are regarded as pathological (Family No. 6, mother).

Fig. 3. Median and semi-interquartile range (shaded) of reflex thresholds in the 200 ears of the control group. Dashed curve indicates limit on and above which threshold value is regarded as pathologically high.

In the genetic series only a few cases were found to fall within this normal range. The stapedius threshold was considerably increased and at many points it could not be reached, even though the hearing thresholds of the subjects almost invariably lay within the normal range (Fig. 2).

It was checked that the cause of the elevation of the reflex threshold was located in the sensory system in the stimulus ear and not due to defects in the motor branch of the reflex arch or the middle ear system of the recording ear.

Such abnormally elevated reflex thresholds—determined on the basis of criteria specified below—were found in 16 fathers and 21 mothers in the parent group. Further details of the distribution of this property are given in Table 2.

Reflex threshold in the control group

Criterion of pathologic limit. That the majority of the reflex thresholds in the hereditary group were elevated was evident from a preliminary inspec-

Table 2. *Distribution of subjects with pathologically high reflex thresholds*

	Hereditary group		Control group	
	Male (n=20)	Female (n=20)	Male (n=50)	Female (n=50)
Younger group	6	11	2	1
Older group	10	10	—	—
Total	37 (62)		3 (3)	

less than 6 dB at the limits of this frequency range (Fig 1) Such dips were recorded in 3 of the fathers (10 per cent) and 7 of the mothers (23 per cent) The dip centre was usually located at 1500–2000 Hz, with a depth of 20–30 dB and a range of about 1 5 octaves There seems to be no correlation between the presence of such dips and the age of the subject they were however found in an appreciably greater percentage of the mothers than the fathers (Table 1)

Hearing threshold in the control groups

The presence of such sub-clinical threshold dips was examined in a control series consisting of 60 women and 73 men ranging in age from 21–24 years The fact that they were found in only one woman and one man (< 2 per cent) indicates that they are normally very rare

While continuous Békésy audiometry is the ideal method for detecting these dips it was considered of interest to examine whether these quite small changes in threshold are recordable by octave audiometry These dips were found in less than 1 per cent of the audiograms for 10 778 14 year-old children (5623 boys, 5155 girls) there was no appreciable sex difference As, however this study was based on the results of octave audiometric screening only dips coinciding with the test frequencies and exceeding 20 dB could be detected Where the anomaly was recorded as present it was confirmed by accurate audiometry

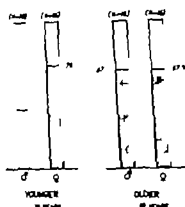
Reflex threshold in the hereditary series

By means of Békésy audiometry it was thus possible in many cases to find in the threshold pattern a peculiarity that would appear to be of an endogenous nature and possibly indicative of endogenous deafness in the carrier In other cases, however no deviant feature was found in the hearing threshold In the subsequent experiments, therefore the auditory system was subjected to tests above the threshold in the hope that further distinctive characteristics might come to light. The test chosen was the stapedius reflex test in which contractions of the stapedius muscle are taken as a measure of the afferent inflow in the acoustic nerve thus providing information on the capacity of the hearing organ at high levels.

It is known from previous studies that the reflex threshold in the frequency range 250–4000 Hz normally lies between 80 and 90 dB hearing level for the various test frequencies

TABLE 1 *Distribution of subjects with hearing-threshold dips*

	Hereditary group		Control group	
	Male ($n = 30$)	Female ($n = 30$)	Male (= 3)	Female (= 60)
Younger group	2	4	1	1
Older group	1	3	—	—
Total	10 (17)		2 (1.5 .)	



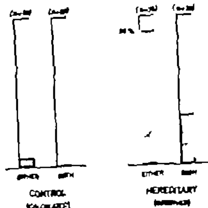


Fig. 4 Fig. 5.

Fig. 4 Distribution of cases with pathologically high reflex thresholds in the two age groups of the hereditary material.

Fig. 5. Observed and theoretical occurrence of pathologically high refle thresholds i one or both marriage partners.

and in 4 subjects of the hereditary series. No appreciable difference in the figures for the two hereditary age groups is noted, however the number of dips was considerably greater for the mothers. As regards the distribution of the dips they were found in one or both partners in 9 marriages (27 per cent) and in both partners in one marriage

The fairly common occurrence of dips in the parent series with a back ground of hereditary deafness, their rarity in the control series, the absence of any evident explanation for them in the medical history and their audiometric configuration all point to a genetic origin.

The occurrence of sujects with pathologically high reflex thresholds are given in Table 2. The distribution with respect to both age and sex was so similar in the two age groups that no lear trend was to be found (Fig 4) In the parent group the peculiarity was bilateral in 3/4 of the cases In the control group th 3 observed cases were all bilat al In the marriages elevated reflex thresholds were found in at least one partner in 27 of them 90 per cent) nd in both partners in 10 (33 per cent) There was no clea difference in this respect between the two age groups.

The par nt group thus contained a much greater percentage of elevated refl x thresh lds than would be expected in a n rmal parent populati n a represented by the control group (Fig) The elevation cannot be ascribed to any known exogenous factor

N le than 7 of the 10 subjects in the parent group where the threshold dip wa found lso recorded abnormally high reflex thresholds. This would indic t that the underlying cause i common to both peculiariti s, and thus constitutes e idence of the individual value of the two tests in detecting subclinical defects in the hearing organ.

tion of the material It is impossible on the basis of earlier data to draw a boundary line between what can be regarded as the normal range and an abnormality and for the same reason as has been given for the hearing thresholds. It was therefore necessary to examine more closely the occurrence of elevated reflex thresholds in persons with normal hearing

The means and ranges for the reflex threshold of the 200 ears in 100 control subjects with normal hearing—50 men 50 women—are reported in Fig 3 The results are largely consistent with earlier experience.

On the basis of the data in Table 3 a criterion for the pathologic limit for the reflex threshold has been formulated

Because of the relatively greater range of the reflex threshold values *for 125 and 4000 Hz these were excluded from the calculations. For the* remaining 6 frequencies (250–3000 Hz) the hearing level chosen as first pathologic reflex threshold value was the next 5 dB step above the P^{90} value for the relevant frequency This necessary escalation to the attenuator stage used in practice means that the first pathologic value will lie at a statistical level corresponding on average to the 94th percentile The pathologic limit so established (= the value for the first pathologic reflex threshold level) is shown in Fig 3

For a subject to be classed as pathologic with respect to the reflex thresholds the pathologic limit should be reached at one ear for 4 of the 6 test frequencies or at both ears for 2 of them This criterion was satisfied by 2 men (4 per cent) and 1 women (2 per cent) in the normal series.

CONCLUSIONS OF THE RESULTS

In the analysis of the results of the hearing tests the parent group was divided into two sub-groups according to age The 15 pairs comprising the younger group had a mean age of 33.2 and 30.3 years for the men and women respectively the corresponding ages for the 15 older pairs were 52 5 and 48.3 years

The presence of threshold dips in accordance with the criteria is shown in Table 1 They occurred bilaterally in one subject of the control group

TABLE 3 *Median 90th percentile and first pathologic level of reflex threshold*

Values giv n in dB he rl g l l (ISO)

Frequency	125	250	500	1000	1500	2000	3000	4000 Hz
Median	6.3	84 2	87 4	85.6	90.5	83.5	82.8	90.7
P^{90}	85.4	91 0	94.8	93.3	97.5	93.0	93 1	101 0
First pathologic level	—	95	95	95	100	95	95	—

however that the stipulation of subjectively normal hearing as a criterion for the hereditary series also is matched by an audiometrically normal hearing acuity age and sex taken into consideration.

The disadvantages of including older parental pairs had to be weighed against the obvious advantages the older group would have had more children, and the hearing of both parents and children could be followed over a longer period. The fact that the parents have had more than one deaf child and that no exogenous cause of the defect can be established is a most reliable indication of genetic defect. A long term study of the child's hearing impairment may provide valuable information on this point a distinctive feature of certain genetic hearing defects is its progressive nature The progress can be slow or with long intervals and a long follow-up period may thus be required for any decision to be possible In the present study 15 of the children with measurable hearing remnants could be followed for more than a decade In 10 of them the impairments were progressive.

The major difficulties of classifying a hearing defect as definitely familial and genetic on the basis of the history and the results of examinations have been dealt with in the Introduction This is not the place for a detailed account of all the factors on which the final decision for each family was based suffice is to state that every effort was made to rule out, so far as our knowledge permits, the possibility that the impairment was other than hereditary Despite this it is possible even probable, that in one case or another an error of judgement might have been made and that the defect was, in fact, of a so far unknown exogenous nature but these cases will be so few as not to jeopardize the validity of results for the group as a whole.

One peculiarity found to occur di proportionately often in the hereditary series was a small but quite distinct dip in the otherwise normal hearing threshold. The dips are situated below 3000 Hz, an area considered not to be ulnerable to exogenous agens. To judge from the approximately similar distribution between the younger and older groups the dips seem to be independent f age on the other hand, in a few cases followed over a long period som increase in the dip amplitude was found

To be regarded as signific nt the dip should meet certain minimum requirement a to its d pth and width Apart from the significant dips the hearing thresholds of other parents contained a number that did not fulfil the criteria e en if these are included the total is hardly overwhelming.

As evidence of a genetic hearing defect the dip is, however most im portant for ther reasons. In sensory-n ural hearing impairment of un expla ned origin that affects y ung and middle-aged person a surprisingly larg proportion ha a basin-shaped audiometric appearance with the centre in the same area as the dips. These defect are often bilateral and a careful analysi will often disclose a high incidence of deafness in the family

Another point th t indicates that this area of the hearing range is

On the basis of our present knowledge it seems that the only explanation one can offer for the presence of these two peculiarities is that they are endogenous They satisfy the criteria for what we define as subclinical defects namely (i) their carriers are unaware of them and (ii) their subtle nature renders them difficult if not impossible to detect with any but refined tests

DISCUSSION

As is seen from the analysis, there was a disproportionately high in cidence of certain peculiarities in the hearing and reflex thresholds in the parent group with a genetic background of deafness peculiarities of such a nature that they cannot be ascribed an exogenous cause.

Perhaps the foremost difficulty encountered in a study of hereditary deafness is to ensure an acceptable selection of families. In this investigation an attempt was made to introduce some measure of randomness in the material by using a group of families residing in a particular geographical area supplemented with new families inserted in the series in the order in which they appeared for consultation irrespective of their domicile This inevitably incurred some degree of skewness as the geographic group was on average older than the chronologic one Since however the recorded hearing defects were most evenly distributed between the two groups it is unlikely that the results would be decisively influenced by criteria of selection

But heterogenous age distribution leads to other difficulties, especially in an attempt to decide whether a subject s hearing may be regarded as normal for his age. For such comparison earlier studies on presbyacusis cannot be used, as these are supposed to exclude all subjects with exogenous or endogenous impairment so as to isolate the hearing loss component ascribed to the aging processes only So far as the parents are concerned it is reasonable to assume that considered as a group they were exposed to the effect of exogenous factors to the same extent as the average in dividual and with a loss in hearing acuity increasing over the years.

For this reason it was chosen to evaluate the parents hearing thresholds against the results of the Wisconsin State Fair Hearing Survey (Glorig et al 1957) in which is given the average hearing acuity in a large series, including also the cases of hearing loss, whatever its cause might have been. The results in this study are reported as median hearing levels for the 500–6000 Hz range as a function of age and sex On this basis of comparison the hereditary series as a whole had definitely better hearing thresholds than the corresponding categories in the WSFHS This is somewhat un expected because about one half of the values should have been located below the median line.

The relatively better hearing acuity recorded in the parent groups is probably fictive and most likely due to the more accurate technique of measurement The result of the hearing threshold examination shows,

TABLE 4 (Cont.)

Family No.	Mode of selection[a]	Parent	Age	Hearing threshold[c]	Threshold dip[d]	Hufle threshold[d]	Hereditary background[e]	Children[f]			
18	Ge	F	46	–	–	–	–	♀ (filled)	♀	♂	
		Mo	42	–	–	+	–	17	13	10	
19	Ch	F	46	–	–		–	♀ (filled)			
		Mo	41	–	–		–	6			
20	Ge	F	49		–	+	+				
		Mo	43		+	+	+	24	20	14	
21	Ge	F	49	+	–	–	+	♂ (filled)	♀ (filled)		
		Mo	48	–	–	–	+	27	22	11	
22	Ge	{F	49	–	–	–		♂	♂		
		{Mo	46	+	–	–	+	26	25	21	13
23	Ge	F	51			+		♂		♂ (filled)	
		Mo	47	–	–	+	+	18	17	15	
24	Ge	F	52		–	+	+		♀ (filled)		
		Mo	43		+	+	+	19	16		
25	Ch	F	52		–	+	+	♂ (filled)	♂		♀ (filled)
		Mo	49			–		20	19	18	10
26	Ge	F	54	–	–		+		♂	♂	
		M	52	–	–	–	+	24	21	17	15
27	Ch	F	51			–	–	♂	♀ (filled)		
		M	57				–	23	14		
28	Ge	F	58	–						⏜ (twins)	⏜ (twins)
		Mo	34					27	24	22	22
29	Ge	{F	67								
		{Mo	63					23			
30	Ge	F	71								
		Mo	61					♂ 32	♂ 41	31	

[a] Ge Geographic Ch chronologic selection
[b] Bracket indicates that the parents are consanguineous.
[c] Hearing loss greater than median for corresponding sex and age group at more than one test frequency
[d] Hearing loss greater than [illegible]
[e] Exceeding the criterion (p. 344)
[e] Hereditary hearing impairment in family. If more than one child is deaf or there is consanguinity between the parents, both parents are scored +.
[f] Filled symbol denotes deaf subject; figures [illegible] age. Brace indicates twins.

34 [illegible]

TABLE 4 *Summary of findings relating to the hereditary material*

Families arranged in order of the father's age

Family no	Mode of selection	Parents[b]	Age	Hearing threshold[c]	Threshold dlp[d]	Reflex threshold[e]	Hereditary background	Children[f]			
1	Ch	Fa	21	−	−	+	+				
		Mo	22	−	−	+	−	3			
2	Ch	Fa	22	−	+	−	+	♀			
		Mo	23	−	+	+	+	3			
3	Ch	Fa	28	−	+	−	−		♂		
		Mo	22	−	−	+	−	3	2		
4	Ch	Fa	31	+ +	−	−	−	♀			
		Mo	29	−	+	+	−	9			
5	Ch	Fa	32	−	−	−	−		♀		
		Mo	29	−	+	+	−	5	1		
6	Ch	Fa	32	−	−	−	+				
		Mo	29	−	−	+	+	7	4		
7	Ge	Fa	33	+	−	−	+	♀	♀	♀	
		Mo	30	−	−	−	−	12	11	6	
8	Ge	Fa	33	−	−	+	+		♀		
		Mo	34	+	+	−	+	15	11		
9	Ge	Fa	35	−	−	−	−	♂	♀		
		Mo	35	+	−	+	+	7	6		
10	Ch	Fa	36	+	−	−	+	♀			
		Mo	29	+	−	−	+	10	6	3	
11	Ch	Fa	36	+ +	−	+	−	♀			
		Mo	26	+	−	+	+	3	1		
12	Ge	F	39	−	−	+	+	♀	♂		
		M	40	+	−	−	+	15	15	9	
13	Ch	Fa	40	−	−	+	+		♀		
		Mo	28	−	−	+	+	9	6		
14	Ge	Fa	40	−	−	−	−			♂	♀
		M	39	−	−	+	+	13	12	10	6
15	Ch	Fa	40	−	−	+	+				
		Mo	39	−	−	+	+	14	12		
16	Ch	Fa	44	+ +	−	+	+		♀		
		Mo	37	−	−	−	+	6	3	1	
17	Ch	Fa	45	−	−	−	−		♂		
		Mo	40	−	−	+	−	11	6		

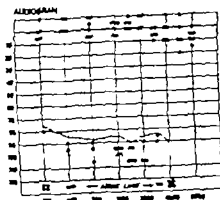


FIG. 6. Hearing and reflex threshold of the six youngest ears in the hereditary group that fall for the reflex criterion. Dash-dotted curve is median of the control group. The lines within the shaded area lie above the pathologic limit.

few acquired defects are known to elevate the reflex threshold, e.g. acoustic tumours, certain viral infections and then invariably in connection with elevation of the hearing threshold.

In the hereditary series there was a high prevalence of elevated reflex threshold which could not be ascribed to a simultaneous proportional elevation of the hearing threshold. This was most striking in the 6 youngest ears, which satisfied the criteria of pathologic limit (Fig. 6). It is thus evident that a completely normal hearing threshold may be accompanied by an elevated reflex threshold, a fact that has not previously been recognized. At the same time as the reflex test affords valuable information in the detection of hidden anomalies in the afferent system of the hearing organ, this observation indicates the need for caution in the evaluation of the reflex test in general recruitment diagnosis.

That the elevation of the reflex threshold was not due to measurement artefact was checked: the sources of error of the method are familiar and have been taken into account (Anderson & Barr 1966). To prove that the reflex recording condition was in order has in most cases been an extremely simple matter as most of the pathologically elevated reflex threshold curves reached the normal limit at at least some frequencies. This unequivocally localized the cause of an elevation to the afferent part of the reflex arc, that is, the cochlea or the acoustic nerve on the stimulated side.

In this study no attempt was made to penetrate further the underlying pathogenesis of the elevation of the reflex threshold, but the obvious connection between this feature and the threshold dips would suggest that they may have their origin in one and the same defect. As mentioned earlier, elevated reflex threshold is generally regarded as one of the symptoms of the retro-cochlear hearing loss. Apart from the elevated reflex threshold the present material, however, revealed no other signs indicating such a site of the defect whether in the form of reduced speech discrimination, thres-

particular susceptible to genetic defects is that a similar centre of impairment has been found in cases of Turner's syndrome The underlying genetic cause here is sex-chromosome aberration In more than 40 per cent of these patients such dips or a basin shaped threshold pattern, centered in the same frequency range, were found (Lindsten 1963 Anderson *et al.*, 1968)

It is rewarding to examine this particular location of the impairment in the frequency range of hearing in connection with certain earlier physiologic and histologic observations The perception of the frequency range in question involves quite a small section of the basilar membrane comprising the upper part of the basal turn and the lower part of the second If it is assumed that the observed peculiarities of the hearing thresholds of the hereditary series have their origin in the cochlea the defect should be situated in this very part of the basilar membrane. This is a site of damage and an audiometric pattern which are distinctly different from the site of the exogenous defects, where it is the more basal parts that are first affected

The same point of onset for genetic hearing defects as reported here has also been demonstrated histologically in waltzing guinea pigs (Lurie 1941) and dogs (Anderson *et al* 1968)

The question why this region appears to be a genetic locus minoris resistentiae can be looked upon in the light of some earlier experimental findings. In normal series of mice (Lorente de Nó, 1933) and oppossum (Larsell *et al* 1944) it has been found by histologic examination that the embryonic development of the receptors in the organ of Corti begins in this region to continue in the basal and apical direction Measurements of cochlear microphonics of the developing rabbit support this view (Änggård, 1965 1967)

The histologic investigations in animals have shown that the genetic defects in the organ of Corti appeared in the very area in which the embryonic development begins, and that the process of breakdown—abiotrophy—probably does not begin until the sensory cells are fully or partly developed (Bosher & Hallpike 1965) There are thus a number of facts that indicate that a hearing threshold defect in the middle frequency range of the hearing may be regarded as indication of a g netic defect in the hearing organ

So far as the search for sub-clinical defects is concerned the stapedius reflex test is in several respects more reliably evaluated than the hearing threshold test The threshold for this reflex has proved to be very little affected by exogenous factors or age Even persons where years of exposure to noise combined with presbyacusis has resulted in a marked elevation of the hearing threshold may record reflex thresholds within normal limits. In this fact lies the value of the stapedius reflex as a test of recruitment the effect of exogenous damage on the hearing threshold is unaccompanied by any effect on the reflex threshold and the resulting reduction in the gap between the two thresholds is assumed to indicate recruitment Only

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ACKNOWLEDGMENTS

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Da die meisten Träger von Erbanlagen rezessiver Schwerhörigkeit nicht in stärkerem Masse Hörstörungen zeigen als die Durchschnittsbevölkerung ist es nicht möglich derartige Erbträger mit üblicher Routine-Audiometrie zu identi fizieren In der vorliegenden Untersuchung wurde nun versucht mit speziellen Testmethoden und zwar mit Hilfe von Békésy Audiometrie und der Schwellen bestimmung des Stapedius-Reflexes, etwaige subklinische Besonderheiten des Gehörs aufzudecken Das Untersuchungsmaterial bestand aus einer Gruppe von 30 Elternpaaren mit normalem Gehör bei denen eine starke Indikation zu erblicher Schwerhörigkeit vorlag. Sie hatten insgesamt 74 Kinder von denen 47 eine schwere erbliche Hörschadigung oder totale Taubheit zeigten Beim Vergleich mit einer normalhörenden Kontrollgruppe konnten in der Gruppe der 30 Elternpaare zwei Besonderheiten in den audiometrischen Befunden festgestellt werden, nämlich kleine aber deutliche Dips im mittleren Frequenzbereich der Hörschwellenkurve und anormal hohe Schwellenwerte fur den akustisch aus-gelösten Stapedius Reflex Anschliessend werden die Beobachtungen im Zusam-menhang mit fruheren genetischen und histologischen Befunden näher diskutiert

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POLYTOME PANTOPAQUE A TECHNIQUE FOR THE DIAGNOSIS OF SMALL ACOUSTIC TUMORS

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Fortunately the day is past when our diagnostic capability was limited to the recognition of patients with advanced tumors who presented with multiple cranial neuropathy and increased intracranial pressure. In no small measure this has been due, in recent years, to advances in the recognition of these tumors by positive contrast material. The polytome pantopaque study is an extension of this work and has allowed an accurate assessment of those patients with small tumors presenting with minimal neurologic and otologic complaints in whom the diagnosis of acoustic tumor is suspect.

The adaptation of microsurgical techniques to the removal of acoustic tumors has made the diagnosis of the small acoustic neuroma more than an academic exercise. The removal of these tumors is now possible with a minimum of neurologic morbidity. This has been emphasized by every recent series in both the otologic and neurosurgical literature (House 1964, 1965; Pool, 1966; Olivecrona, 1967; Drake, 1967).

Before treatment may be undertaken, however, an accurate diagnosis must be made. It is the purpose of this presentation to outline a technique which the authors have found invaluable in the diagnosis of small acoustic tumors. This technique, which we call a polytome-pantopaque study, combines the use of a small aliquot of iophendylate (pantopaque), plain radiographs, and polytome x rays.

The patient with the small acoustic tumor

The complaint of unilateral hearing loss, tinnitus, unsteadiness, or vertigo is usually a symptom that causes these patients to seek medical advice. Unfortunately the audiologic findings in such a patient may be variable (Johnson & Sheehy 1966). The pattern of hearing loss on the audiogram may be minor and can occur at any frequency range. Occasionally the audiogram may be normal. The ability to discriminate the meaning of words is usually impaired to a more marked degree than responses on the plain audiogram, but like the latter may also be normal. Responses of the

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FIG 1 Antero-posterior polytome x ray through the internal auditory canals Note bulbous enlargement of the canal on the left A large air cell is seen over the superior lip of the canal on the right

labyrinth to caloric stimulation may be normal and are more often hypoactive than completely inactive (Hitselberger 1967)

On neurologic examination, decreased facial sensation facial paresis, and cerebellar ataxia are not seen in this group of patients. The only consistent neurologic finding has been decreased sensation along the posterior aspect of the external auditory canal (Hitselberger 1966) This is believed to be due to pressure by the tumor on the sensory portion of the facial nerve in the internal auditory canal Even this finding may not always be present in the patient with a small acoustic tumor

Carefully taken petrous pyramid x rays using the Stenvers Chamberlain Towne and Caldwell views are an important part of the workup Differences of as little as 1 mm between the diameter of the internal auditory canal of the two sides may be of diagnostic significance (Crabtree & House 1964)

Polytome pantopaque

The fluoroscopic iophendylate study of the posterior fossa has proven to be an excellent examination for those patients harboring larger cerebellopontine angle tumors (Scanlan 1964) In comparison with pneumoencephalography this examination has been more accurate and associated with less discomfort to the patient We have not been satisfied, however with the results of this test when dealing with smaller tumors because of the necessity for orientation of the contrast in relation to the surrounding bony landmarks of the internal auditory canal

Polytomography allows the taking of 1 mm x-ray sections through the petrous pyramid in almost any direction (Compere & Valvassori 1964 Mundnich & Freg, 1959) By itself this has been an extremely valuable addition to the radiologic armamentarium because we are able to detect



Fig. 2. Position of patient on x-ray table prior to exposure of polytome rays. Tilting the table downward 35° allows the contrast material to gravitate into the posterior fossa, flooding the cerebellopontine angle and internal auditory canal.

changes in the internal auditory canal and meatus that would not be observed on the conventional plain film (Fig. 1). Large air cells that obscure the internal auditory canal may be delineated. The exact length of the entire canal, as well as the associated structures of the inner ear can be clearly defined.

We have combined polytomography with the use of contrast material in the subarachnoid space. This has allowed us to see both the important bony structures around the internal auditory canal and the tumor outlined by contrast material. This has been especially valuable in the case of small tumors confined to the canal or only slightly protruding into the posterior fossa. In the past these tumors have been inadequately outlined by both pneumoencephalography and iophendylate cisternography.

Technique of Study

The examination is undertaken only after otologic, neurologic, and plain x-ray evaluation have indicated the possibility of an acoustic tumor. Preliminary sedation has not been used. One cc of iophendylate (pantopaque)



Fig 3 Pati t has been returned to horizontal position and turned pro e. The h ad is positioned so that the in lved petrous pyramid is parallel to the x-ray plat

is introduced into the lumbar subarachnoid space under sterile conditions using a no 24 spinal needle *A 1 cc* specimen of spinal fluid is withdrawn *for protein analysis*. The small bore of the spinal needle results in only a minute opening in the dura and arachnoid and does not impair the introduc tion of iodized oil into the subarachnoid space

After the introduction of the *contrast material* the patient is placed *on the x ray table* in the lateral decubitus position with the involved side down The shoulders are firmly secured The table is tilted downward in a cephalad direction approximately 35 (Fig 2) This position allows the contrast material to run up the lateral gutter of the spinal canal into *the posterior fossa flooding* the cerebellopontine angle and internal auditory canal The patient is allowed to remain in this tilted position for approxi mately three minutes so that the iophendylate will migrate upward The table is then returned to a horizontal position and the patient is turned prone The head on the involved side is positioned so *that the petrous* pyramid is parallel to the x ray plate (Fig 3) A plain Stenvers view is exposed at this time In most instances, the tumor will be delineated by this plain radiograph The patient s head is then fixed in position and a series of polytome x rays are exposed through the internal auditory canal

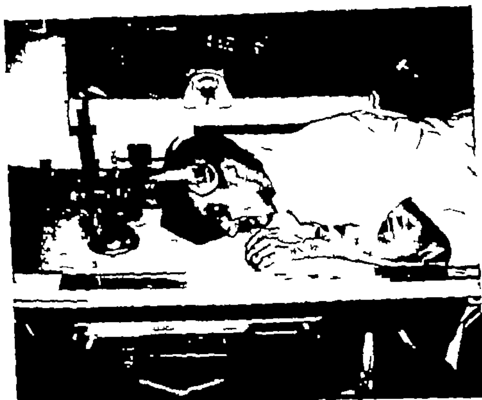


FIG. 4. Fixation of head during xpos re f the polytome -rays.

(Fig. 4) After exposure of the polytome x-rays and the plain radiograph, the contrast material is transferred to the opposite uninvolved side. This is accomplished by hyperextending the patient's head and rotating 13a so that the petrous pyramid of the uninvolved side is placed parallel to the x-ray plate (Figs. 5 and 6) A set of polytome x rays are exposed on this side completing the examination No attempt is made to remove the small aliquot of iophendylate (1 cc) (Figs. 7 and 8)

COMMENTS

Thi technique is adapted to tumors confined to the internal auditory canal or nly slightly protruding into the posterior fossa. The incidence of post pinal headache back and leg ache have been less than 5% of over 200 patients It should be stressed that a small aliquot of contrast material be used, and that this material be placed in the subarachn id compartment with a small bored (no. 24) needle.

Two complication in this series ha prevented filling of the internal auditory anal and cer bellopontine angle



Fig 5 Tran fer of contrast m terial to th opposite sid is ccomplished by hyper-xtending th patient h ad and rotating 135

1 Large osteophytes or hypertrophic disc changes along the spinal axis may prevent the contrast material from entering the posterior fossa In this situation turning the patient supine will allow the contrast material to collect in the posterior fossa
2 If the contrast material is instilled in the extra arachnoid space it will not move and re-injection is necessary

The polytomic pantopaque study is not recommended for tumors that are felt to be of moderate or large size since the area that can be covered by the polytomic field is limited In those patients having V th nerve abnormality in association with deficits in the VIIth and VIIIth nerves, the conventional fluoroscopic pantopaque study will usually delineate the tumor quite satisfactorily since these tumors tend to be larger

The value of the plain radiograph in association with a small aliquot of iophendylate should be stressed In most instances, this single view will serve to make the diagnosis of an acoustic tumor (Figs. 9 and 10)

Hardy & Crowe in 1936, after a detailed study of 250 temporal bones from consecutive autopsies found four histologically verified acoustic tumors These arose deep within the internal auditory canal from the



Fig. 6. The petrous pyramid of the opposite side is positioned parallel t the -ray plate

vestibular portion of the VIIIth cranial nerve and had been overlooked at the time of the initial postmort m examination The largest of these tumors w s 2.5 mm in diamet r In the past, it was believed that acoustic tumors occurred infrequently nd constituted only 5 to 10% of all brain tumors. It is our feeling that the incidence of this tumor is much higher The long ignored wo k of Hardy & Crow would tend to substantiate this view

ZUSAMMENFASSUNG

Verfahren zur radiologisch n Darst llung n Geschwülsten in rhalb des inneren Gehörganges, oder bloss l icht in die hintere Schädelgrube ragend. Eine kleine Menge (1 cc) on Kontrastmaterial, mit dem P lytom Röntgenapparate gibt klares B ld Entsprechend Lagerung des Kranken leitet das k ntrast mat ial, durch Schw kr ft, ufwärts in den Klei hirn-Brückenwinkel. Ein f he V f hme in der St n ers Proj ktion und hn Fluoroskopie wird die Geschwulst gut abgrenzen.

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Fig 7 N rmal polytome pantopaque tudy f the int rnal auditory canal Note the ontrast above nd below the cri ta fal lformi at the lateral end of the canal



Fig. 8. Abnormal polyt m pa t paq tud f the int rnal udit ry nal The med l border of the t m is utll ed by th tra t m terial Th tum r is protrud g slightly int the post ri fossa



Fig. 9. Plain Stenver's projection -ray i association with small aliquot (1 cc) of contrast material. Small tumor is cle rly outli ed protruding from the left int rnal auditory canal.



Fig. 10. Larger tumor utlined by small aliquot (1 cc) of contrast material



Fig. 7 N rmal polyt me pant paque tudy f the int rn l audit ry canal Note the contrast bo and below the crista falciformis at the lateral nd of the canal



Fig 8 Abnormal polytom pa t paq tudy f th int nal udit ry l. The med l border f the tumor i tll ed b th trast mat rial Th tum r is protrudi g slightly i t the posteri fossa

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SURGERY IN PROFOUND HEARING LOSS

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Results are reported in 7 adult cases with profound deafness. Six of them were found on tympanotomy to have otosclerosis and improved after stapedectomy. Tympanotomy was also made on 37 Deaf School pupils who had a similar pattern of hearing, i.e. a severe air conduction loss but some response by bone conduction. Fifty-one per cent of the latter improved by an average of 10 dB or more when tested one month postoperatively. One year later only 1 per cent retained their improvement. It is concluded that all profoundly deaf adult cases responding to some bone conducted sound should be explored; of children, however only those with bone conduction hearing up to 2000 cps are suitable candidates for tympanotomy

Surgery in cases of advanced hearing loss due to stapes fixation has been greatly facilitated by the oval window approach. Exploratory tympanotomy —although a minor procedure—provides definite information on possible middle ear pathology. Hearing may be brought up to the level of maximal cochlear capacity through preservation or reconstruction of the ossicular chain.

Sheehy (1962) recently reported on 15 cases of far advanced otosclerosis. In 3 patients the hearing level was in excess of 85 dB, in 12 there was no response to air conduction, and none responded to audiometer bone conduction. Tympanotomy was made in a total of 26 cases. In 5 the middle ears were without pathology

Obviously in such cases hearing can only rarely be improved to the extent of enabling the patients to discard their hearing aids. However it may improve so much that the patients can use their aids more efficiently than before. This was the main finding in Sheehy's 15 cases, including also 2 in which there was no response to air and bone-conducted sounds preor postoperatively.

This study was initially confined to profoundly deaf adults with suspected otosclerosis and extended to include those pupils of the Oulu School for the Deaf in whom repeated hearing tests pointed to a conductive component. For this purpose 37 deaf children (6 between 7 and 10 years of age, 21 between 11 and 15 and 10 over 15 years) were chosen. The original series of profound hearing loss in adults consisted of 7 persons.

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TABLE 1 *Synopsis of operative results*

	Frequency range – Highest frequency heard – A.C.				B.C.				A.C.[b] 1 month				B.C.[b] 1 year				Changes in frequency range – 1 month[b]		1 year[b]		Changes in threshold dB – 1 month[b]		1 year[b]		Operative findings			Operation		
Total	500	1000	2000	4000	500	1000	2000	4000	500	1000	2000	4000	500	1000	2000	4000	Widened	Narrowed	Widened	Narrowed	Rise ≥10	Fall ≥10	Rise ≥10	Fall ≥10	Normal	Adhesions	Fixation	Stapedectomy	Mobilization	Deliberation
I																														
7	1	1	1	4	1	2	2	2		1		6		1		6	2		2		7		7			1	6	6	1	
II																														
12	8	6			10	2			3	5	2		4	7	1		2		2		5	2		1	1	6	5	3	2	6
III																														
13			13		10	3			2	3	6	2	2	4	6	1	2	4	1	5	7	1	1	1	1	5	7	5	2	5
IV																														
14				14	6	2	2	4		1	3	10		4	4	6		4		8	8		2	1		3	11	7	4	3

[a] Preoperative. [b] Postoperative.

tion. In group II, 2 patients heard the audiometer bone conducted tone at 0 dB setting; this also applies to 3 patients in group III though none heard 2000 cps. In group IV the bone conduction response extended to 1000 cps in 2, to 2000 cps in 2, and to 4000 cps in 4 ears.

Operative findings in group II (12 ears) were as follows: the stapes was immobilized by a network of adhesions in 6 ears but when these were cut and partly removed the footplate appeared mobile. In 5 ears the posterior end of the footplate resisted pressure when its mobility was being tested; 2 ears were subjected to total and one to partial platinectomy, and the remaining 2 ears to simple mobilization. In one case there appeared no tympanic pathology.

In group III, adhesions were removed in 5 ears and the footplate was found mobile. In 7 there was restricted movement: stapes mobilization was performed in 2, of them partial stapedectomy in 2, and total stapedectomy in 3. One tympanum was normal.

Group IV included 3 ears with adhesions and 11 in which the footplate did not move normally. Simple mobilization resulted in good movement in 4 cases, partial stapedectomy was made in 3 and total stapedectomy in 4 ears.

In the whole series of 39 ears, bony footplate fixation of otosclerotic type was found in 2 cases only. The fixation in all others created the impression of fibrous resistance at the footplate margins.

Testing Procedure

Standard audiometric air and bone conduction and speech tests were carried out at intervals to ascertain accuracy loading a special bone vibrator with increased voltage was also used in many cases In addition 256 and 512 cps tuning forks were used to obtain qualitative data anyone not responding to bone conduction for these two forks was considered unsuitable for tympanotomy All patients were tested when leaving the hospital one month postoperatively and after one year

Surgical Technique

An endaural tympanotomy was made with sufficient annular bone removal and the oval window region examined If adhesions were found, these were carefully cut often simultaneously with the stapedius tendon and the mobility of the ossicles and of the footplate was tested In the presence of a mobile chain nothing further was done If the footplate was felt to be fixed, it was either mobilized or removed (in part or totally) If removed *in toto* the window was sealed with fascia and a polythene tube or stainless steel wire inserted from the incus to the graft

Adult cases

The preoperative average hearing levels at 500 1000 and 2000 cps exceeded 90 dB by air conduction in all cases In one the highest frequency heard was 500 cps, in one 1000 cps in one 2000 cps while in four hearing extended to 4000 cps By bone conduction all patients responded to tuning forks and heard at least the low frequencies at the maximum audiometric setting

In 6 cases there was footplate fixation and stapedectomy was done The hearing gain varied in 5 cases from 34 to 70 dB one patient with hearing up to 1000 cps obtained a 20 dB improvement and could start using a hearing aid In the seventh case, with hearing only at 250 and 500 cps, there was advanced tympanosclerosis, and a mobilized footplate was connected to the drum by means of a polythene strut The frequency scale widened from 500 cps to 4000 cps and the average level was 84 dB

These cases are presented as group I in Table 1 It is seen that both the average improvement and the widening of the frequency scale were maintained.

Children

The patients were divided into three groups according to the preoperative range. In Table 1 group II consists of 12 ears in which the highest frequency heard was 500 or 1000 cps, group III of 13 ears with an upper limit of 2000 cps, and group IV of 14 ears with hearing up to 4000 cps. The patients in all groups responded to C_1 and C_2 forks by bone conduc

This favourable result, however was not maintained only 15 per cent of those initially improved retained their gain after one year

The cause of the lost gain is not clear We think that in the majority of our cases there was a small conductive component which was temporarily eliminated in the cases *with numerous adhesions. Since no steroids* were used after operation, it is possible that, similarly as in routine stapedectomies, a number of new adhesions developed postoperatively Another factor seems to be that ligament fixation was the main pathology mobilization, *making the ligament temporarily more yielding, resulted in improved* function. In cases treated by total stapedectomy however none of the above factors should cause a subsequent loss of the gain. Nor can cutting of the stapedius tendon be a cause of either the initial improvement or *later deterioration* at these high intensity hearing levels. *All children had* also been tested on so many occasions that errors due to their inability to perform the test are not likely

In profoundly deaf adult patients tympanotomy seems fully justified if *otosclerosis is suspected Bone conduction* testing with 512 cps fork is generally reliable, whereas the 256 cps fork may cause confusion because its mechanical vibrations are felt on the skull. In children, however the final percentage of improvement is so low that tympanotomy should only be made *if there is amplified* audiometric bone conduction hearing up to 2000 *cps at least. In the less favourable cases it is probably preferable to* perform tympanotomy in adult age when the proliferative tissue response is less marked.

ZUSAMMENFASSUNG

Sieben Erwachsen wurde wegen ine sehr schweren Hörverluste (über 90 dB) operiert. *Otosklerose wurde in 6 Fällen* gefunden, mit *Hörgewinn* nach Staped ktomi Tympan tomie wurde an 37 Kindern ine Taubstummenschule durchgeführt, d ren Hörverluste dieselben F rmen zeigten wie die Audiogramme *von Erw s hsen Bei Kindern wurd ine* Verbesserung von 10 dB oder mehr in 1 nach inem Monat festgest llt doch zeigten nach einem Jahr nur 15% dieser Fälle in permanent Verbesserung. Fast taube Erwachsene mit Gehör *fur in g Knochenleitungstöne sollten operiert* werden Kinder dag ge sollten Knochenl tungshören wenigstens bi 2000 Herz haben, bevor in Tympanotomie indiziert ist

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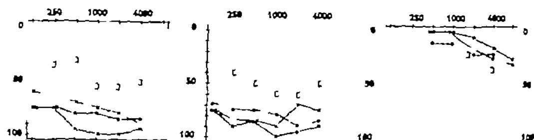


FIG. 1 Three childrens ears with hearing improvement over one year's period. The preoperative air conduction curves (continuous line) for both ears and the postoperative curve (broken line) for the operated ear together with the preoperative bone conduction are shown.

Results one month postoperatively showed that, in group II 5 out of 12 ears had improved by 10 dB or more in group III 7 out of 13 ears, and in group IV 8 out of 14 This improvement was also noticed by the patients themselves and by the teaching staff In the test made one year post operatively however only 3 of the initially improved 20 ears retained their gain. These cases are presented in Fig 1

Histologic examination of the removed pieces of stapes footplate was made in 8 cases. There were signs of cartilaginous degeneration and fibrotic changes in most, but definite otosclerotic foci were present in none

Widening or narrowing of the frequency range following operation occurred in all groups One year after operation 3 of the ears were 10 dB worse than preoperatively This change was also noted in the contralateral ear in 2 cases and was obviously not due to operation

DISCUSSION

Despite the many similarities in audiometric pattern between the adults and children these 2 groups differ in one respect while the former had heard better when young the latter had always been hard of hearing In selecting suitable candidates for operation therefore anamnestic data should be carefully considered

This does not imply that otosclerosis might not start in infancy For instance Whetnall (1953) had in her series 17 hard-of hearing children with parental otosclerosis, the hearing loss being subtotal in 2 Ten years ago, the senior author restored hearing to both ears of a young man who had been deaf from otosclerosis since infancy

In the adult group with 6 otosclerotic ears, one improved from 96 to 26 dB the other 5 improved to or near the level of preoperative bone conduction The change from profound deafness to moderate hearing loss however allowed full rehabilitation with some additional amplification

The results in the group of children seemed very encouraging at first 20 cases out of 39 (51 per cent) showed improvement of 10 dB or more

tions, there has been an interval of at least 2 minutes. Normally the caloric test is performed without the use of Bartels glasses. If however no nystagmus was seen, we applied the glasses to secure detection of even the weakest reactions. The duration of the nystagmus was registered, and we found that in every case with reaction (with or without the glasses) the nystagmus lasted for more than 80 seconds. This is the reason for the below mentioned classification of the intensity of the caloric reactions in which the duration of the nystagmus is not used.

RESULTS

We have grouped the findings in 5 categories

(1) Normal reaction reaction without Bartels glasses as well at 30 as at 44 C.

(2) Reduced reaction reaction at 30 C. At 44 C only reaction with Bartels glasses or no reaction at all at this temperature.

(3) *Markedly reduced reaction no reaction at 30 or at 44 C, but reaction at 20 C.*

(4) No reaction no reaction at 20 C.

In *Table 1* is shown *the results according to this classification*

We have grouped the children in 5 categories, according to the etiology of the deafness, using the classification of Sandberg & Terkildsen (1965) see Table 2

(*a*) Anamneses non-contributory Among the 36 children belonging to this group, the deafness of 15 is caused by hereditary factors, and it is probable that this is also the case in the majority of the rest.

(*b*) *Prenatal origin in all 7 cases, maternal rubella in the first trimester* was registered.

( ) Perinatal origin in one of the cases, a severe asphyxia is the probable reason, the other was a case of erythroblastosis

(*d*) Postnatal origin one case of labyrinthitis, one of encephalitis, and 4 cases of meningitis.

(*e*) Non-classifiable origin cases with several possible explanations of the deafness, in which no distinction is possible.

Table 1. *Results of the caloric test in 55 patients (110 ears).*

Normal reaction	17	(15)
Reduced	58	(54)
Markedly reduced	5	(4)
No reaction	30	(27)
Total (ears)	110	(100)

Table 2. *Classification of the etiology of the deafness.*

Non-contributory	36
Prenatal	7
Perinatal	2
Postnatal	6
Non-classifiable	4
Total	55

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DIFFERENTIAL CALORIC REACTIONS IN DEAF CHILDREN

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Material from 55 totally deaf children is presented The vestibular function has been examined by means of a differential caloric test, using the Hallpike–Fitzgerald method The results are compared with the etiology of the deafness and the changes found at tomography The results appear to differ from earlier findings, as only a few reveal normal reactions. The discrepancies are discussed and it is concluded that a rather close relation exists between hearing impairment and vestibular function

Previous papers on the vestibular function in deaf or hard-of hearing patients are based upon different methods of examination, and consequently not directly comparable Sandberg & Terkildsen (1965) published an extensive survey on the literature, and examined the vestibular function in 57 children from a school for severely hard-of hearing by means of the Hallpike–Fitzgerald method Applying the same technique, we have examined a similar number of children from the State School for Deaf Children in Copenhagen The two materials should make it possible to compare the vestibular function in different degrees of hearing impairment

Our material comprised 55 children, 6–15 years old all totally deaf Apart from having their vestibular function examined, tomography of the temporal bones has been performed

METHOD

Prior to the caloric test otoscopy was performed in order to secure normal ear drums One patient with bilateral perforation was excluded from the material Furthermore the patients were examined regarding spontaneous and positional nystagmus, which was found in 2 cases These patients were also excluded from the material

Both ears were irrigated with water at 30 C for 40 seconds In case of reaction the irrigation was repeated at 44 C also for 40 seconds In cases of no reaction at 30 C, the ear was irrigated at 20 C for 2 minutes (Kristensen 1954) and if any reaction occurred at this temperature, the stooping test was performed If it is a true caloric reaction, the nystagmus will change its direction after tilting the head forward Between the irriga

remnant of hearing the child is referred to a school for severely hard-of hearing from which the material of Sandberg & *Terkildsen* comes. They were able to classify the children in 3 groups according to the hearing, and yet they titled the paper "caloric tests in deaf children" We recom mend that the word deaf be used exclusively in cases of no hearing

As mentioned, we—as did Sandberg & Terkildsen in some of their cases —used Bartels glasses in cases where no nystagmus was seen, or in cases with doubtful reactions. In all the reactions of 39 ears were studied that way Thirty-seven of these ears were placed in the group "reduced" and 2 ears in the group "markedly reduced" In the latter the reactions at 20 were doubtful and the patient would have been placed in the group "no reaction if the glasses had not been used. Application of the glasses in the 37 ears now termed reduced has only influenced the relation between the groups of reduced and markedly reduced reactions, and has not unduely diminished the group of no reaction.

Our results (Table 1) differ somewhat from other authors Sandberg & Terkildsen found 57% with normal reactions. Of the same dimensions are the findings of Shambaugh (1930) Lindenov (1945) Arnvig (1955) and Everberg (1961) whereas we found only 15% with normal reactions. If however we compare our results with the findings in the group with the poorest hearing (more than 98 dB) of Sandberg & Terkildsen's material, there is almost total agreement 19% with normal reactions to our 15% and 23% with no reaction to our 27% As to the disagreement with the findings of the other mentioned authors, several explanations are possible. Partly the methods are not identical with ours, apart from Everberg's, whose material on th other hand, is different from ours, and partly there is no detailed information about the hearing. As just shown, there is a close relation between the degree of the hearing impairment and the vestibular function, and it is highly probable that the average hearing in the othe materials is better than in ours, and thus explaining the discrepancies between the findings. Everberg (1961) states that partial loss of estibular function in connection with deafness is rare This we have not been able to confirm, as we in 85% of the cases find a more or less reduced activity of the estibular organ.

In Table 3 a comparison between the etiology of the deafness and the vestibular function is made It is interesting that the prenatal group which exclusi ly comprises cases of prenatal rubella, no cases of severely impaired vestibular fun tion are recorded This is in accordance with the fi dings of Sandberg & Terkildsen and Arnvig. In accordance with Linde no are th findings in the cases of postnatal, i.e. acquired deafness, among which th re are no cases with normal vestibular reactions

Table 4 gi es a comparison between the radiological findings and th vestibular function Some of the findings are published (Jensen, 1967) nd the rest will be published in detail later It is seen that while the relative amount of cases with normal function is the same in the 2 groups,

TABLE 3 *Comparison between the etiology of the deafness and the vestibular function*

	Prenatal	Perinatal	Postnatal	Non-contributory	Non-classifiable	Total (ears)
Normal reaction	5	1	0	7	4	1
Reduced	9	1	5	43	0	58
Markedly reduced	0	0	0	3	2	5
No reaction	0	2	7	19	2	30
Total (ears)	14	4	12	72	8	110

TABLE 4 *Comparison between the radiological findings and the vestibular function*

	Tomography normal	Tomography pathological	Total (ears)
Normal reaction	11 (1 %)	6 (16)	17
Reduced	41 (60)	14 (36)	58
Markedly reduced	2 (5 %)	3 (12 ,,)	5
No reaction	17 (20)	13 (36 ,,)	30
Total (ears)	74	36	110

In Table 3 the vestibular function is compared with the etiology of the deafness

As mentioned tomography of the temporal bones has been performed in all the children In 20 of the patients (36 ears) some sort of pathological changes of the inner ear was found. In 34 of these ears, the findings must be considered as congenital malformations of either the cochlea or the vestibule/semicircular canals, or both In one patient osseous obliteration of the entire labyrinth due to labyrinthitis was found Table 4 is a comparison between the radiological findings and the vestibular function

DISCUSSION

The pupils at the State School for Deaf Children in Copenhagen are nowadays totally deaf They are referred from the State Hearing Center Copenhagen, which only refers children without any useful remnants of hearing They do not respond to shouting and the audlograms show in only a few cases any remnants of hearing at or above 1000 Hz. Below 1000 Hz, there are none with a hearing better than 80 dB Moreover it is probable that the obtained audiograms in most of the cases is only a manifestation of sense of vibration and not an expression of any real hearing

According to Everberg (1961) the term deafness is not well-defined He advocates the use of the word only in cases where no hearing is left, and we feel it justified to apply the term on our material In cases of any

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THE ACOUSTIC MIDDLE EAR REFLEX IN UNANESTHETIZED RABBITS

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It is demonstrated that the response of the acoustic middle ear reflex can be recorded in awake rabbits by measuring the change in the acoustic impedance in a way similar to what has been done in man. The excitability of the reflex was measured in the frequency range between 500 and 3000 cps. The reproducibility of the measurement in the same rabbit is in the order of 3 dB over a period of one month, whereas there is a considerable individual variation. It was found that the excitability of the reflex is slightly higher when activated by ipsilateral than by contralateral stimulation. It was further shown that the reflex exhibits no appreciable fatigue during 1 minute stimulation with a 2000 cps pure tone.

Anesthetized animals have frequently been used in studies on the function of the middle ear reflex although it is known that the anesthesia affects the reflex. In some studies anesthetics have been avoided and decerebrated or decorticated animals have been used instead (Lorente de Nó, 1933, Wersäll 1958). Although the effect on the middle ear reflex of decerebration or decortication may not be as severe as anesthesia, it can not be taken for granted that the function of the reflex is the same as in an unanesthetized normal animal.

In most studies on the activity of the middle ear muscles in unanesthetized animals implanted electrodes have been used either in order to record the action potentials of the two muscles individually (Bornschein & Krejci, 1952, Wersäll 1958, Salomon, 1966) or in order to record changes in the cochlear microphonic potential (Galambos & Rupert, 1959, Simmons, 1959, 1962, 1964, Hilding, 1960). Recordings of the electrical muscle activity show the relation between the activity of the two muscles but do not provide direct information about the changes in the middle ears acoustic performance caused by the activity of the muscles. Furthermore, the electromyographic activity in the two muscles may appear before muscle contraction has influenced the acoustic properties of the middle ear. The change in the cochlear microphonic potential on the other hand provides precise information about the net change in sound transmission caused by the activity of the two muscles. Both methods, however, imply chroni-

the group with the pathological tomographic findings comprises more cases of pronounced impaired vestibular function than the group with no radiological changes In 3 ears a severe malformation of the lateral semicircular canal was found and none of these responded to the irrigation. In the case with bilateral osseous obliteration no function was present.

CONCLUSIONS

The present investigation confirms the conclusion of Sandberg & Terkildsen that there is a parallelism between hearing loss and vestibular function Our material consists of children who are totally deaf and this probably explains why we only find 15% with an intact vestibular apparatus, a very low figure compared with earlier findings It should also be noted that further evidence is given that the vestibular function is not completely extinguished because of prenatal rubella Finally it is shown that there is no close relation between vestibular function and radiological (osseous) malformations of the inner ear However it should be noted that in 3 ears with malformations of the lateral semicircular canal no response to the caloric test was found

ZUSAMMENFASSUNG

Die Vestibular Funktion wurde mit differential kalorischer Prüfung von Hallpike–Fitzgerald bei 55 tauben Kindern untersucht Die Ätiologie der Taubheit und die tomographischen Veränderungen werden mit der Vestibular Funktion verglichen Die Reaktion wird nur in einzelnen Fällen als normal befunden was mit früheren Untersuchungen nicht übereinstimmt, und die fehlende Übereinstimmung wird diskutiert Daraus folgert, dass eine enge Verbindung zwischen Vestibular Funktion und dem Ausmass der Taubheit besteht.

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cally implanted electrodes which may *affect the reflex action* In some animal experiments, finally the tension of the two muscles was recorded with the aid of strain gauges attached to the muscle tendons (Lorente de Nó & Harris, 1933 Wersäll 1958)

The characteristics of the acoustic reflex of the rabbit has earlier been investigated in acute animal experiments by Lorente de Nó & Harris (1933) Wersäll (1958) and Price (1963 *a* *b*) The former used decorticated animals in which the responses of the muscles to pure tone stimulation were recorded by myographs. Wersall (1958) used rabbits under light barbiturate anesthesia and recorded the muscle action potentials as well as the tension of the muscles Price also used animals under light barbiturate anesthesia and recorded the change in the cochlear microphonic potential as a sign of activity of the middle ear muscles elicited by contralateral stimulation In the early investigations by Lorente de Nó *et al* the stimulus strength was not given in terms of absolute sound pressure level as was done by Price and Wersäll Price found that the curve for the threshold of the middle ear reflex as a function of frequency runs almost parallel to the ear s sensitivity curve determined as the sound pressure required to produce a standard cochlear microphonic potential. The difference between the sound level which produced a cochlear microphonic potential of 10 μV and the threshold of the reflex was found to be 45–50 dB In man the curve showing the sensitivity of the middle ear reflex at various frequencies, expressed as the intensity required to produce a given small impedance change was also found to be almost parallel to the audibility curve for frequencies up to 4000 cps (Jepsen 1955 Møller 1962 *a*)

The results given by Price on the sensitivity of the rabbits ear in terms of cochlear microphonic and on the sensitivity of the reflex were obtained in experiments on different ears. He recorded the change in the cochlear microphonic potential caused by middle ear muscle activity elicited by a sound in the opposite ear The reflex threshold was defined as that sound intensity which was sufficient to produce a measurable change in the cochlear microphonic potential

In man measurements of the changes in the ear s acoustic impedance are regarded as a convenient method for the study of the action of the middle ear muscles (Metz, 1946 Jepsen 1955 Møller 1958 1961 1962 *a* *b* Terkildsen & Nielsen 1960 Klockhoff 1961) and has also been applied in experiments on anesthetized cats (Gisselsson Löfström & Metz, 1957 Møller 1964) Quantitative studies on *unanesthetized* animals however have not previously been performed

The change in the ear s acoustic impedance to sound stimulation is a graded response which expresses the change in the acoustic properties of the middle ear caused by middle ear muscle activity and the measurements of changes in the acoustic impedance can be made on awake animals since they do not require any surgery

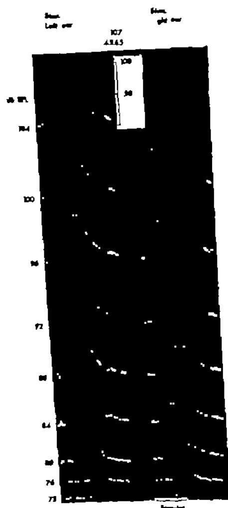


Fig. 1 Impedance change both ears I response to 200 cps pure ton of 200 msec duration pplied t the left ea (left col mn) and t the right ear (right column) Solid lines represent impedance chang in the l ft ear and the dashed lines how impedance cha ge the right ear The scale the pper right corner gi es the impedance change in per cent of the ma imal obtained hange. The stim lus strength i dB re. 0.0002 b I show to the left

The present paper deals with a study on the properties of the acoustic middle ar r flexes in unrestrained awak rabbits, the change in the coustic impedance being used as a measure of the net activity of the two middle ear muscles. The change in acoustic impedance was measured on both ears imultaneously when the acoustic reflex was elicited by presenting sinusoidal sound timuli to one ear t a time. In that way the crossed and th uncrossed reflexes were tudied independently

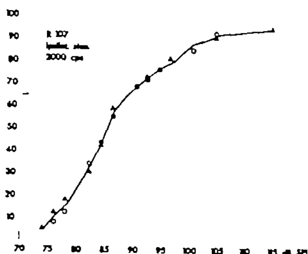


Fig 2. Ipsil teral impedance chang in per cent of maximal obtainable cha ge as a function of stimulus intensity measured when the stimulus intensity was raised st pwise (triangles) and when it w s low red stepwise (circles) The solid line shows the mean of su h pairs f determinations.

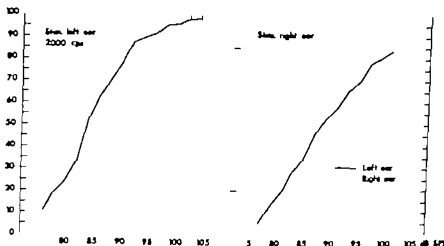


Fig. 3 Impedance change as a fu tion of stimulus sound pressure le l f 2000 cps pure tone with a duration of 200 msec. Th refl x response in both ears i shown when either the left r the right ear w s stimul ted.

METHODS

Seventeen rabbits weighing between 1 2 and 3 5 kg were used in a total of 81 experiments No albino rabbits were used

Rubber tubes were inserted in the ear canals and two identical impedance measuring devices were attached to these tubes The tubes were secured in the ear canals by means of a dental molding material (Lastic 55) which within a few minutes provided a rubber like mold Although the mold did not adhere to the walls of the ear canal it was held firmly in position because of the irregular shape of the ear canal and it could be removed easily at the end of the experiment.

The rabbits were sitting in a small box open at the top They were not in any way tied and they usually sat quietly during the experiment which

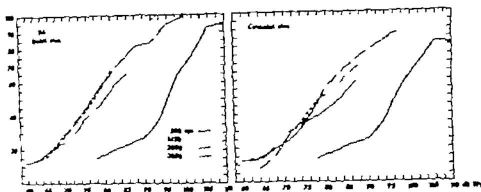


Fig. 4. Impedance change function of stimulus intensity f for different frequencies of 500 msec pure tones. The results are from one experiment.

could last several hours. In some of the experiments the position of the pinnae together with the impedance measuring devices was fixed by means of a piece of foam plastic in which carvings for the pinnae were made

A sound source for eliciting the acoustic middle ear reflex was included in the impedance measuring device (Møller 1961) Pure tones, varied in steps of 2 or 4 dB were used (200 or 500 msec duration) The rise time of the tone to 90% of maximal amplitude was 2 msec and the time of decay to 10% of the maximum value was 2 msec. The sound stimulus was presented alternatively to the left and right ear while the intensity was increased stepwise from below the threshold of the reflex to the maximal intensity employed, and then lowered stepwise to values below the threshold. Thus the same intensity was presented twice to each ear

The methods of recording the change in the ear's acoustic impedance were the same as that used in previous investigations on man (Møller 1961 1962 b) *The acoustic impedance change* was measured at a frequency of 800 cps. This sound was on continuously during the experiment and its sound pressure level was approximately 60 dB, re 0.0002 μb, i.e. well below the r flex threshold. The impedance of the ear was balanced out electrically in th absence of stimulation and the change in the acoustic impedance appeared as a 800 cps signal, th amplitude of which was proportional to the magnitude of the changes in the ear's acoustic impedance Recording were made from both ears simultaneously by means of two identical impedance measuring devices (see abov) The responses w re ecorded n magnetic tape during the experiments and the data was processed at later occasion.

The sound pressure level near the eardrum of the tone stimulus was measured when the pparatus was in place in the ear canal by using the earphone which during the impedance measurements supplied the 800 cps t n a microphone (see Møller 1961) Such measurements were always perf rmed at the end of each experiment and in many cases also at the beginning of the experiment.

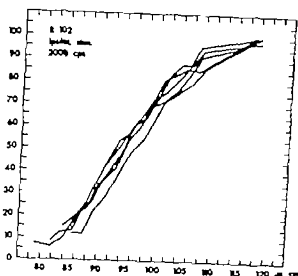


FIG. 5. Impedance change as a function of stimulus intensity measured in one rabbit at different occasions during one month. The stimulus was a 2000 cps pure tone and the ipsilateral response is shown.

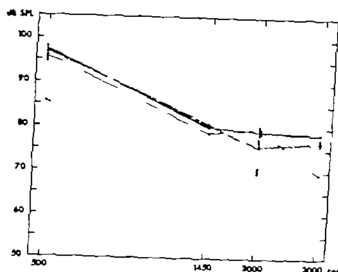


FIG. 6. The sensitivity of the ipsilateral reflex as a function of frequency obtained in 11 rabbits expressed as sound intensity required to produce 20% of the maximal obtainable impedance change. The connected symbols represent values obtained during the same experimental session in four different rabbits.

RESULTS

Fig. 1 shows the acoustic impedance changes in both the left ear (solid line) and the right ear (dashed line) in response to a 2000 cps pure tone of 200 msec duration. The two columns of records show the responses elicited from the left and right ear respectively. The records of the impedance changes in the two ears were aligned with respect to amplitude in such a way that the maximal obtainable impedance change gave the same size of deflection in the two channels. This was accomplished in connec-

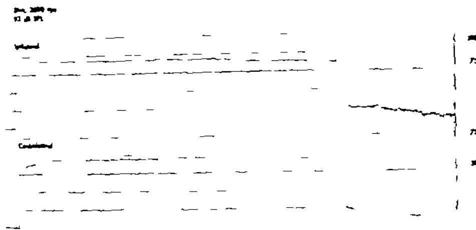


FIG. 7 Impedance chang in both ears as functio f time licited by one minute continuous pure tone with frequency of 2000 cps. The scales t the light gi the impedance hange in per cent of the maximal btainable change.

tion with processing the data from the magnetic tape As is seen the impedance change increases with increasing stimulus strength and the impedance change for a certain stimulus intensity is larger in the ipsilateral than in the contralateral ear The shape of the curves having equal amplitude is similar both for ipsilateral and contralateral stimulation.

The magnitude of the impedance change measured immediately before th termination of the stimulu and expressed in per cent of maximal obtainable ipsilateral response was plotted as a function of the stimulus intensity (Fig 2) The triangles in Fig. 2 represent the amplitudes of the responses btained when the timulus intensity was raised stepwise, and the circles represent the values obtained when the stimulus was lowered stepwise The lack of hyst resis shows that the *results were not affected* by fatigue or facilitation The mean of such pairs of values fall along a curv (solid line) which shows the impedance change as a function of timulus intensity (given in dB relative 0.0002 μb (SPL))

Fig 3 shows the amplitude f the reflex response in both ears as a function of stimulus intensity when the left or the right ear were stimulated. The diagram show that within th whole intensity range investigated the ip ilateral reflex requires a lower sound intensity than the contralateral for the same response Th mean of this difference measured at 20% of maximal impedance hange obtained in a total number of 68 experiments, is 2 dB anging from −3 dB to +7 dB.

Fig 4 shows the impedan changes as a function of stimulus intensity for pure tones f four different frequencies. There is no significant dif ference in the slope of th curves. One would expect that the curve for the higher timulus frequ ncies should be steeper than that for the lower fre-

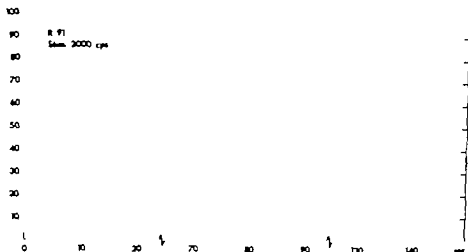


FIG. 5 Impedance change in the ipsilateral (upper row of points) and contralateral ear (lowe row) to repetitive stimulation with 2000 cps ton burst of 200 msec duration at a rate f 1 pe second.

quency (500 cps) since a contraction of the middle ear muscles provides a greater decrease in sound transmission at low than at high frequencies and thus extends the intensity range of the middle ear reflex at low frequen cies This unexpected result illustrated in Fig 4 will be dealt with in the discussion

In order to determine the day-to-day variation of the reflex function, 4 rabbits were tested with intervals of one day to several months The variations were found to be independent of the length of the interval and the range was 3 dB Fig 5 shows a typical family of five stimulus response curves of the ipsilateral reflex obtained in one animal at different occa sions during one month As seen there are shifts within a range of 3 dB without any change in slope The response varies more near threshold *than at response values above 20% and the variation of 3 dB refers to the* responses between 20% and 70% impedance change Thus, the reproduci bility is good and the accuracy of the measurements is in the order of magnitude with which the sound pressure level of the stimulus can be controlled

Fig 6 shows the sensitivity of the ipsilateral reflex as a function of frequency obtained in 11 rabbits. The connected symbols represent values obtained during the same experimental session The sensitivity is expressed as the stimulus intensity required to produce 20% of the maximal obtain able impedance change As seen the threshold expressed in this way (cf Møller 1961) is nearly constant between 1450 and 3000 cps while at 500 cps it is about 15 dB higher

Response to Long Duration Stimulation

Fig 7 shows the impedance change in response to continuous stimulation with a tone with a frequency of 2000 cps and a duration of 60 sec. The stimulus intensity was 93 dB SPL or approximately 20 dB above the reflex

threshold. Both the ipsilateral and contralateral stimulation are followed by a sustained response which does not show any significant change during stimulation. It should also be noted that after termination of the stimulus the relaxation of the muscles is much slower than after stimulation of short duration (cf Fig 1) Finally the amplitude of the responses to repetitive stimulation with tone bursts of 200 msec duration (frequency 2000 cps) presented at a rate of 1 per second is plotted versus time in Fig 8. As seen, there is only a slight diminution of the amplitude of the impedance, the reduction, after 140 seconds of stimulation, being only 10% of maximal obtainable impedance change This value corresponds to a decrease in the sensitivity of about 3 dB both on the ipsilateral and contra lateral side

DISCUSSION

The present investigation shows that the acoustic middle ear reflex can be investigated on awake, unrestrained rabbits with the aid of the technique which has been used in humans without any surgery The functional characteristics of the acoustic middle ear reflex in rabbits, covered by the present study shows great similarities in general with those of the human middle ear reflex studied with the same technique As in humans, the ipsilateral reflex has a higher sensitivity than the contralateral the mean difference being about 2 dB in rabbit (Fig. 3) compared with 2–14 dB in man (Møller 1961) The sensitivity of the ipsilateral reflex measured as the intensity required to produce 20% of the maximal obtainable impedance change was found to be 70–80 dB SPL for frequencies between 1450 and 3000 cps and 85–100 dB for 500 cps (see Fig. 6) These values are roughly 10 dB lower than the corresponding values for humans at 1450–3000 cps and lmost identical t 500 cps.

Price (1963) measured the sensitivity of the contralateral middle ear reflex in the rabbit by recording the change in the cochlear microphonics. Since his experiments were performed on lightly anesthetized preparations, the slightly higher threshold values that he obtained for the contralateral reflex seem to be due to the effect of the anesthetic drug.

According to studies on the cat with other methods for recording the muscle activity the magnitude of the reflex response is highly variable. The reflex exc tability has thus been reported to depend on such factors as the animals att ntion, tate of wakefulness, etc. In the present study the response measured t different occasions sh wed very little variations and th reproducibility corresponded to the accuracy with which the sound pressure f the stimulus could be reproduced from time to time. The high degree f reproducibility does not directly rule out the possibility that the reflex response may vary due to variations in the attention and alertness. However it seems unlikely that it should be possible to perform a great number f xperiments over a long period of time with the animal in the same state of lertness and attention.

Wersäll (1958) who measured the tension of the tympanic muscles in animals under light anesthesia and on decorticate animals showed a considerable fatigue when sounds of high intensity were used. He further reported that weaker sounds did not produce any appreciable fatigue which is in accordance with the results of the present investigation

It is known that the contraction of the middle ear muscles decreases the transmission of low frequencies through the middle ear and thus reduces the volume displacement at the oval window Therefore one would expect that the slope of the stimulus response curve at a low frequency should be less than at higher frequencies as is actually the case in man As mentioned above no such difference in the slope was found in the present investigations on rabbits (see Fig 4) This somewhat unexpected result may be explained by the fact that the frequency range within which a contraction of the tympanic muscles reduces the middle ear transmission can be expected to be greater in the rabbit than in man (Møller 1965) It is therefore possible that in rabbit the effect of reflex on the middle ear transmission is almost the same within the entire frequency range investigated It is also possible that the relationship between the magnitude of the volume displacement of the *cochlear fluid* and the reflex contraction varies as a function of frequency

ACKNOWLEDGMENTS

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ZUSAMMENFASSUNG

Es wird gezeigt, dass in der gleichen Weise wie es in früheren Arbeiten schon für das menschliche Ohr beschrieben worden ist, das Verhalten des akustischen Mittelohrreflexes auch beim Kaninchen durch Messung der Änderung der akustischen Impedanz untersucht werden kann Das Kaninchen ist dabei vollkommen wach und in seiner Bewegung nicht beschränkt Die Empfindlichkeit des Reflexes wurde im Bereich zwischen 500 und 3000 Hz gemessen Die Reproduzierbarkeit bei Messungen an dem gleichen Kaninchen lag in der Grösse von 3 dB über den Zeitraum eines Monats, dagegen zeigte sich eine beträchtliche interindividuelle Variation Die Messungen ergaben ferner dass die Empfindlichkeit des Reflexes etwas höher bei ipsilateraler Aktivierung war als bei kontralateraler Stimulation Des weiteren konnte auch festgestellt werden dass der Reflex bei Beschallung von 1 min Dauer mit einem 2000-Hz Ton kein merkliches Abklingen zeigt

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THE SPIRAL GANGLION IN PROFOUND DEAFNESS

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The spiral ganglion cell population was evaluated in 41 ears from 29 profoundly deaf patients. In 10 ears 66 to 100 per cent of the spiral ganglion cells remained in 3 ears 33 to 66 per cent of the cells remained and in 28 ears less than 33 per cent remained In all of these ears there was severe atrophy of the organ of Corti When the etiology of the deafness is known it often is possible to predict the condition of the ganglion An excellent ganglion cell population would be expected if the deafness was due to ototoxic drugs and a severe loss of ganglion if due to bacterial labyrinthitis.

Profound deafness means the absence of detectable hearing by routine testing methods For practical purposes it can be regarded as total Sensory deprivation be it auditory visual or some other modality has a remarkable effect on the reactions of the entire individual Profound deafness is a particularly depressing psychological condition largely related to the feeling of social isolation Despite lip reading instruction and general supportive measures these individuals tend to become secluded, lonely and often dispirited Anything that might help them to re-establish sonic contact with the outside world would be of value The ability to hear and discriminate normal speech is the most desirable objective but even indistinct speech would help to facilitate lip reading The ability to hear such sounds as the closing of doors might relieve the feeling of isolation

Direct stimulation of the cochlear nerve has been considered for many years as a possible means of providing hearing for some of these individuals and some reports of such attempts have been published (Djourno *et al* 1957 Doyle *et al* 1964 Simmons, 1966) In all of these the ability to hear some sounds has been accomplished although such complex activities as

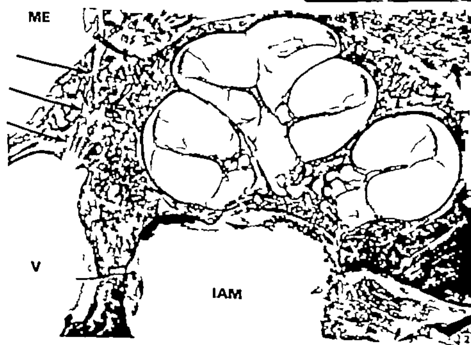
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[2] Chief of Otolaryngology M ssa husett Ey nd Ea Infirmary Prof sor f Ot logy and Laryngology Harvard Med cal School, Bost

F g 1 The spiral g nglion of cat with in r a concussi n without skull f cture resulting from a head blow (Schuknecht *e l* 1951) Beha l l test perf med 3 months afte the injury showed th nimal t be tot lly d f H t logic tud h wa almost complet disappearance f the rgan of Corti but few piral ga gli n lls remain Each neurone has a n rmal appe ing ent al a n but th peripheral fiber i





missing ad large lear acuol is located at the peripheral pole f the neurone ar ues

Fig. 2. Trans erse fracture of the temporal bone, patient (D.D.). Death occurred 4 months ft this f act re as the res lt of nother accident. The fracture line, indicated by rrows, extends from the middle ar (*ME*) through the estibule (*V*. *IAM* Int rnal uditory meatus.

speech discrimination were not achieved. Recent studies on stimulus coding in single fibres of the auditory nerve suggests the possibility of development of prosthetic devices that could convert sound energy into patterns of electrical impulses similar to those found in that nerve (Kiang, 1965). A problem will remain in getting this coded pattern of electrical impulses into the appropriate functioning fibers of the eighth nerve. Our concern in this publication is not in the technical aspects of stimulation of the nerve but in the availability of nerve fibers to be stimulated.

For any method of direct excitation of the eighth cranial nerve to succeed in transmitting complex signals, there must be an adequate population of functioning cochlear nerve fibers. Therefore an attempt was made to determine the ganglion cell population (and thus the auditory fibers) in ears showing profound deafness from various etiologies. This would establish the feasibility of direct stimulation in these cases.

The assumption that the spiral ganglion population reflects the numbers of auditory nerve fibers is supported by histological studies in animals and humans. It is a known fact that when the central fibers of the spiral ganglion cells are injured the cell bodies of the involved neurones will degenerate in 2 to 3 weeks. Similarly when the peripheral fibers are injured, the cell bodies of the injured cells usually disappear. It has been noted that a few may remain possibly as many as 10% in certain disease conditions. In these ears the cell body is shrunken with a pyknotic nucleus. There is an intact central axone and a vacuole at the pole representing the location of the missing peripheral axone (Fig. 1). We believe that in the determination of functional neural units the error introduced by counting cell bodies rather than peripheral nerve fibers is not greater than 10%.

PROCEDURE AND RESULTS

The temporal bone collection of the Massachusetts Eye and Ear Infirmary contains over 500 sets of specimens with documented histories. This study has included only those ears where direct stimulation of the cochlear nerve would have been a practical possibility. Thus those cases were excluded where the deafness was due to acoustic neurinoma or where life expectancy was limited because of severe congenital abnormalities or secondary malignant lesions in the temporal bone. In the collection there are some cases where total deafness was present for less than 3 months before death, and these also have been excluded because the time lapse may have been insufficient for degenerative changes to have been completed. The total number of suitable ears in the Massachusetts Eye and Ear Infirmary collection is 34 and to these are added 7 ears from the University of Chicago's collection to give a total of 41 ears from 29 patients.

The serially sectioned temporal bones were examined and the spiral ganglion cell population estimated for several regions of the cochlea

TABLE 1 *Ganglion cells supplying the 11 to 24 mm region of the cochlea*

Etiology	Ganglion cells present A. 2/3 to normal	B. 1/3 to 2/3	C. Less than 1/3	Total
Congenital	2	—	2	4
Transverse fracture	1	—	—	1
Bacterial labyrinthitis	—	1	16	17
Viral labyrinthitis	3	1	5	9
Congenital syphilis	—	—	2	2
Vascular	—	1	1	2
Kanamycin intoxication	2	—	—	2
Otosclerosis	2	—	2	4
Total	10	3	28	41

The 11 to 24 mm regions of the cochleas are determined from graphic reconstructions according to the well established methods described by Guild (1921) and Schuknecht (1953). This region of the cochlea is most important for speech reception based on current knowledge of the spatial distribution of frequency response in the human cochlea.

(1) the region from about 11 mm to 24 mm along the organ of Corti, corresponding to that part of the cochlea most important for speech reception (500 cps to 4000 cps) (2) the basal turn, basal end to about 18 mm (3) the middle turn, about 18 mm to 28 mm, and (4) the apical turn from about 28 mm to the apical end, which is located at about 32 mm.

The assessment of the numbers of spiral ganglion cells is based on experience developed in the study of several hundred ears by the authors and the final estimates were determined by mutual agreement. Although the counting of ganglion cells would increase the accuracy this degree of precision was not required for this study.

It seems likely that the various neural units may have been assigned different functions, for it has been established that the peripheral axones have several different types of distribution e.g. some end mainly on inner hair cells and others mainly on outer hair cells (Fernández, 1951). Therefore if the degenerative process should involve the selective loss of a functional type of neurone, the psycho-acoustic manifestations would reflect this selectivity. For these reasons we believe that attempts to closely correlate ganglion cell loss with functional deprivation is of limited value.

To minimize the dangers of incorrect assessment, the estimates have been limited to expressions in thirds of normal, i.e. (*a*) more than 2/3 of the normal number present, (*b*) between 1/3 and 2/3 present and (*c*) less than 1/3 remaining. The findings are summarized in Table 1 following which is a more detailed description of the pathological changes in the various disease conditions for which specimens were available.

TABLE 2 *Congenital*

		Cochlea turn		
	11 to 24 mm	Basal	Middle	Apical
K F Sch lbe 1	A	A	A	A
C. N Schelbe 2	A	A	A	A
C. G Schelbe 3	C	C	C	C
P M. Mondlnl	—	B	—	—

It is not po sibl to determine the peech frequ ncy area of th cochlea f this e r

Congenital deafness

A detailed discussion of the pathological findings in profound congenital deafness is beyond the scope of this present communication which is limited to those ears in our collection from patients who had a normal life ex pectancy at birth The data is shown in Table 2 and includes 3 ears with cochleo-saccular aplasia (Scheibe) of genetic etiology and one with Mondini type aplasia (single cochlear coil) from 4 patients

It is encouraging to note that 2 of the 3 ears with the Scheibe defect have at least 2/3 of the normal number of spiral ganglion cells, and the ear with Mondini type aplasia has a good population in the only existing turn of the cochlea

Transverse fracture of the temporal bone

The transverse fracture of the temporal bone occurs perpendicular to *the long axis of the petrous pyramid and traverses the vestibule of the* inner ear resulting in degenerative changes in the sensory structures, usually with complete loss of cochlear function (Grove 1939 Proctor *et al* 1956) One such ear in our series has a good population of nerve fibers (Fig 2 and Table 3)

Bacterial labyrinthitis

Bacterial labyrinthitis is a common cause of bilateral profound deafness, usually occurring secondary to either otitis media or meningitis. In the 17 ears studied there is severe destruction of the membranous labyrinth usually with severe loss of the spiral ganglion (Fig 3 and Table 4) In most of these ears there would be no possibility of achieving any useful hearing by direct stimulation of the cochlear nerve

TABLE 3 *Fracture*

		Cochlea turn		
	11 t 24 m	Basal	M ddl	Apical
D D	A	A	A	A

TABLE 4 *Bacterial labyrinthitis*

			Cochlea turn		
		11 t 24 mm	Basal	Middle	Apical
F B.	R	C	C	C	C
	L	C	C	C	C
E.D	L	C	C	B	B
F F	L	C	C	C	C
G H.	R	C	C	C	C
	L	C	C	C	C
M.O	R	B	C	A	A
Z.S	R	C	C	C	C
L Z.	R	C	C	C	C
	L	C	C	C	C
E.McM	R	C	C	B	A
	L	C	C	B	A
M.McK	R	C	C	B	A
C.G	R	C	C	C	C
	L	C	C	C	C
C.K	R	C	C	C	C
	L	C	C	C	C

Viral labyrinthitis

The hearing loss in viral infections of the labyrinth range in severity from mild to total and of the latter 9 ears from 6 patients are available for study

The comm n factor in all cases is degeneration of the organ of Corti which i more marked in the basal turn. The extent of degeneration of the spiral ganglion usually parallels the degree of damage to the supporting cell of the organ of Corti There is an obvious exception to this in the mumps labyrinthitis case (Lindsay *et al* 1960) in which there is total absence of the organ of Corti in the basal turn on both sides with the presence of an almost normal number of cochlear neurones.

Viral labyrinthitis apparently can produce all degrees of inner ear change f om mild lesions f the basal turn to severe diffuse destruction of the organ of Corti Thus the amount of spiral ganglion available in these ears cannot be predicted accurately and this is obvious from the data in Table 5 Wh reas proof of the viral tiology for th case of sudden deafness is lacking, the pathological changes re similar to those occurring in known mumps and measles labyrinthitis.

Syphilitic labyrinthitis

Some patients with congenital syphilis develop a profound bilateral hearing loss and histological studies f ears from such indi iduals show degenerative changes in the organ of Corti (Karmody & Schuknecht, 1966) In this series there are 2 ear from 2 patients with congenital yphilis, both

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	11 to 24 mm	Basal	Middle	Apical
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P M Mondini	—	B	—	—

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TABLE 4 *Bacterial labyrinthitis*

			Cochlea turn		
		H.L. 24 mm	Basal	Middle	Apical
F.B.	R	C	C	C	C
	L	C	C	C	C
E.D.	L	C	C	B	B
F.F.	L	C	C	C	C
G.H.	R	C	C	C	C
	L	C	C	C	C
M.O.	R	B	C	N	N
Z.S.	R	C	C	C	C
L.Z.	R	C	C	C	C
	L	C	C	C	C
E.McM.	R	C	C	B	N
	L	C	C	B	N
M.M.K.	R	C	C	B	N
C.G.	R	C	C	C	C
	L	C	C	C	C
C.K.	R	C	C	C	C
	L	C	C	C	C

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Viral labyrinthitis apparently can produce all degrees of inner ear change from mild lesions of the basal turn to severe diffuse destruction of the organ of Corti. Thus the amount of spiral ganglion available in these ears cannot be predicted accurately and this is obvious from the data in Table 5. Whereas proof of the viral etiology for the case of sudden deafness is lacking, the pathological changes are similar to those occurring in known mumps and measles labyrinthitis.

Syphilitic labyrinthitis

Some patients with congenital syphilis develop a profound bilateral hearing loss and histological studies of ears from such individuals show degenerative changes in the organ of Corti (Karmody & Schuknecht, 1966). In this series there are 2 ears from 2 patients with congenital syphilis, both

TABLE 5 *Viral labyrinthitis*

			Cochlea turn		
	11 to 24 mm	Basal	Middle	Apical
N A. R Measles	C	C	C	C
L	C	C	C	C
R O R Measles	C	C	C	C
I	C	C	C	C
R.P I	C	C	C	C
P C.[b] I Sudden deafness	B	B	B	A
A.M[d] R Rhino-pharyngitis	A	A	A	A
A W[d] R Mumps	A	A	A	A
L	A	A	A	A

G eek (1961)
[b] Schuknecht *et al* (1962)
Beal *et al* (1967)
[d] Lindsay *et al* (1960)

exhibiting marked damage to the organ of Corti and corresponding degeneration in the spiral ganglion (Table 6)

While acquired syphilis only rarely affects the labyrinth similar degeneration takes place (Goodhill 1930) and therefore it can be anticipated that patients totally deaf from syphilis will have a degenerated spiral ganglion and are unlikely to benefit from attempts at direct stimulation of the cochlear nerve.

Kanamycin intoxication

The ototoxic effect of certain antibiotics have been known for over 20 years (Brown & Hinshaw 1946) and streptomycin was used as early as 1948 for the destruction of the vestibular endorgans in the treatment of Menière s disease (Fowler 1948) With the passage of time there was an increasing number of clinical (Glorig, 1951) and experimental (Berg, 1949)

TABLE 6 *Syphilis*

			Cochlea turn	
	11 t 24 mm	Basal	Middle	Apical
L.F L	C	C	B	B
E.M. L	C	C	C	C

FIG. 3 Bacterial labyrinthiti has resulted in compl t lo f the rgan of Corti a d near t tal loss f spiral gangli n cell (pati nt C. K.) Th scal contain fibro s tiss and bone (*B*) *IAM* Internal audit ry m atus

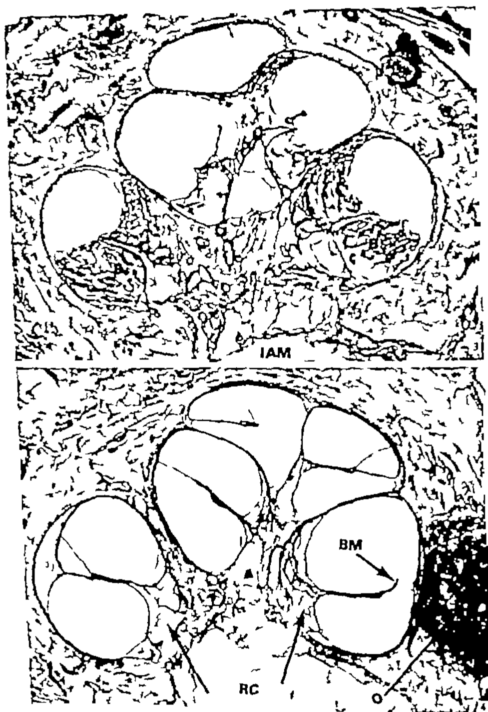


Fig. 4. Otosclerosis associated with profound deafness (patient A. B.). The basilar membrane (BM) is ruptured in the region of spiral ligament atrophy adjacent to the otosclerotic focus (O). Only a few spiral ganglion cells are seen in Rosenthal's canal (RC).

TABLE 7 *Ototoxic drugs*

	11 to 24 mm	Cochlea turn Basal	Middle	Apical
L. C. R	A	A	A	A
L	A	A	A	A

reports of damage to the labyrinthine structures following the administration of antibiotics, but it was not until 1960 that histological findings were reported in the human (Lindsay *et al* 1960) This case demonstrated severe hair cell damage following the administration of neomycin with lesser degrees of degeneration of the supporting structures and good preservation of the spiral ganglion

Since then further histological reports have appeared on the effect of several "mycin" drugs on humans (Benitez *et al* 1962) and animals (McGee & Olszewski 1962 Ward & Fernández, 1961 Farkashidy *et al.*, 1963) Although there is some variation the overall consensus of opinion is that the hair cells of the organ of Corti especially the outer hair cells, are the most susceptible to the ototoxic effect of these drugs. The supporting cells are involved occasionally especially after high dosage of the drugs. It is also apparent that the ganglion cells survive when the supporting cells are not damaged

Table 7 shows the findings in the spiral ganglion in patient L C. who was given 12 grams of kanamycin during an 8 day period for the treatment of pyelonephritis She died 3 months later of kidney failure (Igarashi & Yoshinobu 1963)

The histological findings in intoxication with quinine (Rüedi *et al* 1952) and nitrogen mustard (Cummings) show a similar tendency to destruction of the hair cells with little or no damage to supporting cells and good ganglion cell population if their corresponding supporting cells have escaped damage

It is to be expected therefore that in most patients with deafness due to the administration of ototoxic drugs, a good population of spiral ganglion cells will be present

Vascular occlusion

In this series there are 2 ears from a patient who experienced 2 episodes of sudden complete and permanent hearing loss. The first at the age of 52 in the left ear and the second at 65 in the right ear She suffered 2 cerebro-vascular accidents after the age of 60 years and died of bronchopneumonia at 85 years of age

From the history and histological findings, the etiology is presumed to have been vascular occlusion In the left ear the damage to the organ of

TABLE 8. *Vascular*

			Cochlea turn	
	11 to 24 mm	Basal	Middle	Apical
B.W. R	B	B	B	A
L	C	C	C	B

Corti is reflected in the spiral ganglion in which there are a few ganglion cells at the basal end where the sensory endorgan is completely missing. There is a moderate population at the apex where the damage is less severe. The findings are shown in Table 8.

Even when histological studies are available it is not possible to state with certainty the cause of sudden deafness in all cases. The decision as to the etiology must be based on associated findings such as peripheral vascular occlusion, strokes, or myocardial infarction.

Otosclerosis

Sensorineural deafness in association with otosclerosis is a common finding but there is much controversy as to whether there is an etiological relationship or whether the perceptive loss is simply coincidental. This point has been discussed at great length elsewhere (Schuknecht, 1966 Schuknecht & Cross, 1966 Lindsay & Beal, 1966 Wolff 1966 Altmann 1966 Nager 1966 Linthicum, 1966 Rüedi & Spoendlin 1966) and will not be dealt with here except to consider those cases in which there is profound hearing loss in association with otosclerosis. While it appears unlikely that otosclerosis frequently affects the function of the inner ear there is no doubt that it can do so.

In this series there are 4 ears from 3 patients with profound deafness presumably due to otosclerosis and the findings are shown in Table 9.

In the right ear of patient A B there is severe atrophy of the organ of Corti and spiral ganglion and rupture of the basilar membrane presumably due to extreme atrophy of the spiral ligament (Fig. 4). The other 2 ears in this group show moderate degeneration of the organ of Corti

TABLE 9. *Otosclerosis*

			Cochlea turn	
	11 to 24 mm	Basal	Middle	Apical
A.B. R	C	C	C	C
L	C	C	C	C
F.A. R	A	A	A	A
V.R.A.	A	A	A	A

but the most striking finding is atrophy of the spiral ligament with rupture of the basilar membrane accompanied by good preservation of the spiral ganglion

On this evidence of 4 ears, the spiral ganglion may be severely degenerated or well preserved but there are no clinical means of predicting the situation

CONCLUSIONS

The plight of the totally deaf is such that any sonic contact with the outside world may help Some attempts at direct stimulation of the eighth cranial nerve have been reported and while many problems remain, there is hope that this procedure can be developed to be of some value for these unfortunate individuals.

If any method of direct stimulation is to succeed in transmitting complex signals such as speech an adequate population of functioning auditory nerve fibers will be necessary Experimental studies have shown that pure tone thresholds may be normal when no more than 25% of the spiral ganglion cells remain in the region of the cochlea serving the frequencies being tested (Schuknecht & Woellner 1953) The number of ganglion cells required for socially adequate hearing for speech has not been determined however studies in progress in our laboratory by Otte suggest that a ganglion cell population in the speech frequency area of the cochlea which is 2/3 or more of normal can provide useful speech reception

We have evaluated the ganglion cell population and thus the auditory fibers of the eighth nerve, in ears having profound sensorineural deafness of various etiologies to establish the possibilities of direct stimulation in these patients.

The patterns of degenerative change in the spiral ganglion were consistent for some etiologies and inconsistent for others It appears that the spiral ganglion population can be expected to be good in ears profoundly deaf from some genetic types of congenital deafness, temporal bone fractures, and ototoxic drugs A poor population of ganglion cells would be expected in profound deafness due to bacterial labyrinthitis and congenital syphilis. When profound deafness is due to viral labyrinthitis, vascular occlusion or otosclerosis, the extent of degeneration of the ganglion is variable and there is no clinical means of assessing the population of the remaining ganglion cells

In our series of 41 ears from 20 profoundly deaf patients, there were 10 ears with more than 2/3 of the spiral ganglion cells remaining 3 with 1/3 to 2/3 remaining and 28 with less than 1/3 remaining If we assume that 2/3 or more of the spiral ganglion cells are needed for useful speech reception given a physical means of reproducing cochlear function, then 10 of 41 ears, or 25% meet the selection criterion When the etiology of the deafness is known however the ability to predict the condition of the ganglion is greatly improved An excellent population of ganglion cells

would be expected if the deafness was due to ototoxic drugs and a severe loss if due to bacterial labyrinthitis.

Fewer ganglion cells are required for the identification or differentiation of simple acoustic stimuli such as the telephone bell, slamming doors, or thunder than for speech and probably even fewer are needed for the detection of noise.

Of that total of 41 ears we have found 13 to have less than 10% of the ganglion cells remaining, and of these, 9 have less than 1% remaining. Although it is presently not possible to predict the potential for electrical stimulation in ears with ganglion cell losses of these magnitudes, it is certain that the complexity of stimuli which can be impressed upon the acoustic nerve and transmitted to the brain depends upon the number of available functional neural units.

ZUSAMMENFASSUNG

Die Spiralganglionzellbevölkerung wurde in 41 Ohren von 29 hochgradig schwerhörigen Patienten eingeschätzt. In 10 Ohren blieben nur 66 bis 100 Prozent, in 3 Ohren ... 33 Prozent und in 28 Ohren weniger als 33 Prozent der Spiralganglionzellen erhalten. In all diesen Ohren wurde eine schwere Atrophie des Corti'schen Organs festgestellt. Wenn die Ätiologie der Schwerhörigkeit bekannt ist, ist es oft möglich auch den Zustand der Spiralganglien vorauszusagen. Eine ausgezeichnete Ganglionzellbevölkerung kann man erwarten, wenn die Schwerhörigkeit durch ototoxische Medikamente bedingt ist und ein schwerer Verlust von den Ganglionzellen durch bakterielle Labyrinthitis verursacht ist.

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THE EFFECT OF WATER IMMERSION ON PERCEPTION OF THE OCULOGRAVIC ILLUSION IN NORMAL AND LABYRINTHINE DEFECTIVE SUBJECTS[1]

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The separate and combined influences of otolith and nonotolith sensory inputs upon perception of the oculogravic illusion were investigated by manipulating the visual and gravitoinertial force environments. By comparing the visually perceived direction of space by four naval aviators and four deaf persons with bilateral labyrinthine defects when dry and when immersed in water up to neck level, the contributions of (1) field force receptors in the vestibular organs and (2) nonvestibular proprioceptors stimulated by external contact support could be differentiated. Under these various conditions it was found that in normal persons, the vestibular contribution is predictable in terms of the direction of the gravitoinertial force vector but that the nonvestibular contribution varies; it may be relatively great or small. In persons with bilateral labyrinthine defects a nonvestibular contribution was always present but there was great individual variance. The significance of the findings in terms of tests measuring the function of the otolith organs is discussed.

This report describes an experiment in which sensory inputs influencing the visually perceived direction of space were measured. A person is poised to perceive these influences if, for example, he is subjected to centripetal force while in a fixed position on a human centrifuge. The change in direction of the gravitoinertial vertical with reference to his body is rightly interpreted as a tilt away from the upright, and the visual framework tends to tilt concordantly. The latter phenomenon is a form of apparent motion which for convenience has been termed the oculogravic illusion (Graybiel, 1952).

This illusion, first described by *Purkinje* (1820), was the object of investigation by Mach (1875) who reasoned that it must have its genesis in a sensory organ in the skull, and the nonacoustic labyrinth was implicated. *Kreidl* (1892) regarded the illusion as having its origin in the vestibule

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Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

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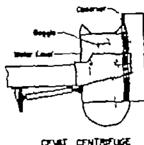


Fig. 1 Gondola for h man centrif gatio nder wet nd dry conditions.

their significant clinical findings are summarized in Table 1 All had suffered from meningitis in childhood, one at pre-school age Their otolith function was determined by means of ocular counterrolling. The counterrolling index (CI) is defined as one-half the sum of the maximum rightward and leftward ocular counterroll when the subject is tilted 25 50 and 75 from the upright. Typical values for normal and L D subjects do not overlap (Miller II & Graybiel 1963) The L-D subjects were thoroughly familiar with all aspects of the experiment except those dealing with centrifugation under water

The aviators, 26 to 32 years of age, were in excellent health and perforce had met the stringent medical requirements for duty involving flying None had a history of middle ear disease. Routine hearing and caloric tests revealed no significant abnormality Their counterrolling indices, obtained at 50-degree maximal tilt, ranged from 241 to 434 All were experienced in taking tests of many kinds, but none was familiar with the procedures in thi experiment.

Apparatus

The heavy duty centrifuge at General Dynamics Astronautics (San Diego, Calif) was modified for our purpose. It was hydraulically driven, with adequate performance characteristics and excellent rotary coaxial connections. A gondola was fabricated that consisted of a cylindrical tank and observer s platform mounted in a trunnion 18.08 feet from the center of rotation (Fig. 1) It was equipped with a suitable water heater closed circuit television, and voice communication system By means of a pneumatic piston the wh l assembly could be rotated about th trunnion pins through an arc of 45 in a period of 30 seconds with the centrifuge stationary or rotating Inside the tank a metal seat was fitted to a rail system and could be removed, along with the subject, by means of a hoist. Bolted to the seat was the rear half of a Fiberglas body mold prepared for each subject the front half was secured by "quick release" m tal locks.

A isual test goggle (VTG) was devised which represented a modification f a visual target device used previously (Clark & Graybiel, 1952) On the

(otolith apparatus) when 13 of 62 "deaf mutes failed to perceive it Our early experimental findings (Graybiel 1956) using deaf persons with bilateral labyrinthine defects (L-D subjects) seemed to confirm Kreidl's work with minor qualifications. Later in a systematic study the settings of 10 L-D subjects were compared with those of nine normal subjects under identical conditions (Graybiel & Clark 1965) The normal subjects readily perceived the apparent rotation of the target (oculogravic illusion) and their estimates bore a meaningful relation to the angular changes in the gravitoinertial horizontal Individual variance in these subjects was manifested chiefly in their overestimation of the illusion when they were exposed to relatively large changes in direction of the force vector None of the L D subjects made settings comparable to those of the normal subjects The only consistent L D performers were four who perceived little or no illusion the others expressed varying degrees of difficulty in making the settings which were characterized by inter and intra individual variance

Although the inferior performance of the L D subjects was ascribed to loss of otolith function, there was no correlation between the magnitude of the settings and the degree of ocular counterrolling a measure of otolith function (Woellner & Graybiel 1959 Miller II 1962) It was hypothesized that the differences among the L-D subjects in perceiving the oculogravic illusion might be explained by residual otolith function, by inputs from nonotolith proprioceptors or by a combination of both

The present experiment was designed to test this hypothesis by exposing normal and L D subjects to centrifugation under dry condition and when immersed in water Field force receptors in the otolith organs would not be affected by the immersion while nonotolith proprioceptors mechanoreceptor systems, would be minimally stimulated

Two classes of phenomena relating to visual space perception can be studied while systematically manipulating the force environment One class deals with "interactions in which cues to a visual frame of reference are available, the other with "influences" in which visual cues are either lacking or inadequate In the present experiment we took advantage of the extraordinary circumstance in which a dim line of light in darkness is an inadequate cue yet can be manipulated to indicate the visually perceived direction of space In using such a visual target influences" are being studied Their threshold of effect i e the threshold for perception of the oculogravic illusion under ideal conditions, is a change in direction of the gravitoinertial horizontal of approximately 1 5 (Graybiel & Patterson Jr 1955)

PROCEDURE

Subjects

Four naval aviators and four deaf persons with bilateral labyrinthine defects participated The four L-D subjects were in good general health

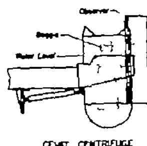


Fig. 1 Gondola for h man centrifugatio under w t and dry conditions.

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A visual test goggle (VTG) wa devised which represented a modification of a visual target device used previously (Clark & Graybiel 1952) On the

TABLE 1 *Clinical findings in four deaf subjects with bilateral labyrinthine defects*

Subject	Age	Onset of meningitis, age	Cochlear function[a]		Semicircular canal function[b]		Otolith function[c] body tilt	
			R	L	R	L	±50	±75
JO	36	7½	Nil	Nil	Nil	Nil	126	1 6
MY	26	8	Nil	Nil	Nil	+ at 60 sec	63	82
PE	35	12	Nil	Nil	Nil	Nil	21	30
ZA	23	3½	+ > 135 dB	+ > 130 dB	Nil	Nil	14	36

[a] Response to white noise up to 160 dB.
[b] Response to irrigation with water at 3 C±1 for 3 minutes.
[c] Ocular counterrolling index. (See text.)

right side of the device a red Maddox lens illuminated by a collimated light shining through a pinhole aperture produced a line against a dark background the left side was an opaque eye covering The lens could be rotated clockwise or counterclockwise about its center by means of a knurled knob An external counter on the VTG displayed the meridional position of the target line to the nearest 0 1 which was relayed via a closed-circuit television system to the control room

Method

The subjects task described elsewhere in more detail (Graybiel & Clark 1965) consisted essentially in setting the target line, on demand to the horizontal of extrapersonal space It should be noted that under all wet conditions, the subject s head was out of water and that he had to raise one hand above water to adjust the knob on the VTG In other words, there was not total immersion Under stationary conditions the experimenter offset (rotated) the target switched on the light, and the subject set it to the horizontal and signaled completion The average of five such settings under prerotation conditions was used as the 'perceived horizontal (PH) with which to compare subsequent settings The centrifuge then was brought up to speeds causing a change in direction of the gravitoinertial horizontal (GIH) of 10 20 or 30 in periods of never less than 20 seconds. The order of exposure involving the three changes in GIH was varied randomly among the eight subjects and among the five test sessions for any given subject After constant rotation for at least an additional 20 seconds the target light was switched on and the subject was signalled to make the first of the five settings

Five series of trials, either under "wet" or "dry" conditions, were con

Table 2. Perception of the oculogravic illusion in normal and labyrinthine-defective subject Mean and standard deviation of five settings

s = Perceived horizontal.

Conditions	Change in gravitoinertial horizontal	Normal subject: CI s	CI σ	DI s	DI σ	HU s	HU σ	LP* s	LP* σ	Labyrinthine-defective subject: JO s	JO σ	MY s	MY σ	PG s	PG σ	ZA s	ZA σ
Wet-BT Series I	0		1.1		0.5		1.3		1.0		1.9		0.8		5.0		1.3
	10	3.6	2.9	10.1	1.9	+ 9.0	1.7	6.8	1.7	+ 1.9	1.2	+ 3.6	1.7	+ 8.3	4.8	− 4.1	2.7
	20	17.3	3.7	23.8	1.3	+ 19.8	1.7	8.5	4.7	+ 1.1	1.1	2.0	5.0	+ 4.1	3.6	+ 10.5	2.2
	30	40.3	4.9	36.1	1.9	23.8	1.2	1 1	6.4	+ 3.7	1.6	+ 2.0	3.9	− 0.2	3.2	+ 18.0	3.1
Wet-BT Series II	0		1.1		0.9		0.5		0.7		0.8		1.8		1.9		0.9
	10	8.3	2.0	11.0	0.8	9.0	0.8	12.9	1.5	− 1.8	0.8	+ 2.1	2.8	− 15.0	7.7	+ 8.1	1.4
	20	20.6	1.6	21.1	0.6	20.8	1.3	14.8	1.8	− 2.8	0.9	+ 2.2	3.9	− 21.0	3.4	+ 17.3	2.3
	30	31.9	1.9	37.3	1.1	32.1	2.5	18.6	1.8	− 1.1	1.0	+ 2.5	1.8	− 11.7	3.9	+ 20.0	1.0
Wet HS	0		2.4		0.9		1.0		1.1		0.0		1.7		2.0		3.0
	+ 10	+ 15.4	5.0	+ 8.4	1.2	+ 6.8	0.6	+ 1.6	1.6	+ 3.5	2.0	+ 1.0	1.9	+ 6.1	0.9	− 2.1	2.4
	+ 20	+ 20.2	4.8	20.1	0.9	+ 22.8	2.0	16.4	2.1	+ 3.4	1.9	+ 9.1	1.5	+ 1.8	1.9	+ 5.1	0.5
	30	28.5	5.0	+ 37.2	0.5	+ 39.8	1.5	8.4	2.6	+ 6.6	1.5	+ 7.7	4.2	+ 10.1	1.5	− 2.9	2.8
Dry Series I	0		1.0		0.1		0.5		0.9		2.2		1.3		3.4		1.9
	+ 10	+ 19.0	3.8	+ 12.7	1.0	+ 6.8	1.2	− 21.5	0.8	1.1	1.2	+ 5.6	2.0	+ 8.2	1.6	+ 7.8	1.1
	+ 20	+ 35.3	2.8	+ 27.7	1.0	+ 18.9	1.5	− 20.1	1.9	0.0	1.1	+ 5.9	0.3	+ 6.8	1.3	+ 27.0	2.8
	+ 30	+ 47.5	3.4	38.7	1.0	+ 33.3	2.1	10.3	1.8	+ 4.1	3.5	+ 11.7	1.5	+ 17.4	1.8	+ 41.1	3.8
Dry Series II	0		0.7		1.2		0.1		3.1		1.1		2.0		2.4		1.3
	+ 10	+ 11.2	3.1	11.1	1.1	+ 9.4	1.5	− 10.8	2.5	+ 2.2	1.3	+ 1.0	2.8	+ 2.2	1.1	+ 10.0	2.9
	20	34.2	1.8	23.1	0.6	+ 21.1	1.7	+ 10.1	2.9	6.7	1.0	+ 9.0	2.1	+ 11.5	2.0	+ 22.6	1.9
	+ 30	51.9	2.7	+ 37.9	0.7	+ 31.7	4.8	15.5	4.0	+ 12.7	1.1	+ 14.7	2.7	+ 22.7	3.1	+ 25.1	3.3

* Subsequently dropped from the normal group. See text and Fig. 2 D.

ducted in the following order In the first two the subjects wore bathing trunks and the tank was filled with water up to their necks this was termed the water or "wet BT" condition In the third and fourth series the subjects wore bathing trunks, and the tank was empty this was referred to as dry' or "air" conditions. A fifth series under wet conditions, not originally contemplated required the subjects to wear a foam rubber suit. This was termed the wet RS condition

Manipulating the force environment is neither easy nor precise if comparison is made with manipulation of visual or auditory environments In the present experiment the use of individually fitted molds ensured good positioning of the subject in the force environment under all conditions and excellent contact with his support under dry conditions

RESULTS AND DISCUSSION

The actual settings made by all subjects under all conditions in this experiment are shown in Table 2 Positive and negative values indicate respectively rotation of the target in the same and opposite direction to that of the gravitoinertial horizontal during positive accelerations.

It is seen in Table 2 that the settings of the normal subjects demonstrate a consistent and regular dependence on changes in the GIH in three but not in the fourth subject, LI The bizarre settings in the case of LI were wholly unexpected requiring individual consideration and necessitating his removal from the normal group

In Fig 2 A is shown a comparison between the means of the settings made under dry and wet conditions by each normal subject All subjects demonstrated an increasing tendency toward higher values in their settings for equivalent increases in change of direction of the GIH This well known tendency has been termed the magnitude effect (Graybiel & Clark 1965) reflecting the progressively greater increase in magnitude compared with increasing angle of the gravitoinertial force vector the positive acceleration of the curve depicting magnitude becoming substantial at 15 and rising rapidly after 30 Only CU demonstrated significant differences between the settings made in dry and wet conditions In the former he greatly overestimated the angular change in GIH at all three levels, while under wet conditions the overestimation was made only at 30 and the amount was moderate Thus it would appear that water immersion reduces the magnitude of the oculogravic illusion by reducing nonotolith sensory inputs Stated differently nonotolith sensory inputs contributed significantly to the perception of the illusion by CU but not by DI or HU

The bizarre settings in the case of LI are depicted in Fig 2 B When questioned, he stated that he had experienced no difficulty in making the settings and considered his performance satisfactory

The four L-D subjects manifested such great inter and intra individual

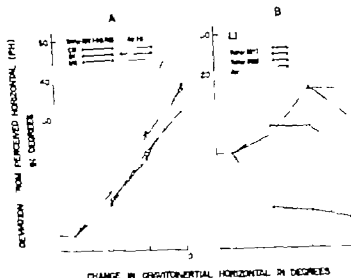


Fig. 2. Subjects estimates of the horizo tal plotted gainst changes in the gra it inertial horizontal during centrifugation under dry and water immersion conditions. Subjects were exposed to change I direction of the force ector with reference t themsel es in the frontal plane. They indicated the horizontal by rotating dim line of light in darkness. (A) Settings made by three subjects constituting the ormal group. Each point under wet conditions represents the mean f 15 settings in three perimental trials nd under dry conditions the mea of 10 settings in tw trials. (B) Atypical set tings was subject with normal estibular functions as indicated by caloric tests and ocula counterrolling.

variances that they are considered separately The settings made by JO are depicted in Fig 3 A The curves representing the values under wet BT conditions indicate that he did not perceive the illusion hence there is no evidence using this indicator that he possesses residual otolith function Under wet RS conditions the settings suggest that he may have perceived the oculogravic illusion In the *first* series of trials under dry conditions the only evidence that JO may ha e perceived the illusion was the apparent magnitude effect at 30 The curve representing the *second* series under dry conditions clearly indicates that JO perceived the illusion. Although this later curve shows values far below the expectation for normal subjects, its configuration is typical of one from a normal subject. Among our entire group of L D subjects (10) JO is one of two persons whose behavioral responses lea t resemble those of the normal, although he has the highest counterrolling index (Miller II & Graybiel, 1963)

The findings in the case of MV Fig. 3 B, clearly indicate that he perceived the illusion under dry but not wet BT conditions. His settings made under wet RS conditions are irregular but suggest that he may have perceived the illusion. These results show that otolith influence on the illusion was not

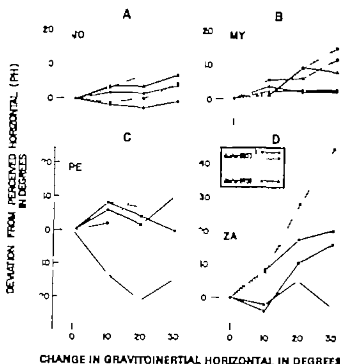


FIG 3 Estimates made by four deaf subjects with bilateral labyrinthine defects (L-D) Conditions the same as described for Fig 2. Each point represents the mean of five settings.

present but that there was evidence of influences from nonotolith sensory inputs under dry and possibly under wet RS conditions.

The settings made by PE, Fig 3 C, demonstrate that he readily perceived the illusion under dry conditions When submerged PE stated that at times, he was confused and did not know which way was up this was reflected in the greater variance in his settings than in those of the others Under wet BT conditions the curve depicting his *first* series of trials indicates that the illusion may have been perceived minimally at 10 and 20 but not at 30 while in the *second* series his settings were discordant In the wet RS series PE probably perceived the illusion at 10 and 30 but not at 20 These findings under wet conditions suggest a loss or reduction of nonotolith influences on perception of the illusion The loss of "contact cues caused disorientation which may have contributed to irregularities in his making the settings

ZA s settings (Fig 3 D) under dry conditions show not only that he perceived the oculogravic illusion, but also, that his estimates were similar to those of the normal subject CU Under wet BT conditions he perceived the illusion but considerably underestimated the change in angle in the gravitoinertial horizontal Under wet RS conditions he did not perceive the illusion at 10 and 30 and whether he perceived it at 20 is doubtful Among all of our L-D subjects, ZA s responses most nearly resemble the

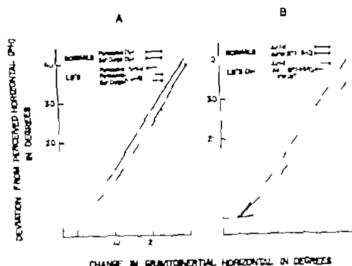


FIG. 4. (A) Comparisons between settings made nder dry conditions in San Diego and Pensacola. Solid lines compare (w rmal groups composed of differe t subjects. The four L-D subjects participating at San Diego were part of the larger Pensacol group. (B) Comparison bet een mean settings made by ormal and L-D bjects under wet and dry conditions.

normal. This similarity was not apparent initially when he was a participant in our other experiments but seems somehow to have been acquired as a result of practice That he was the youngest among all the L-Ds at the time *he acquired his vestibular defects (3 / years) may have been a factor*

In Fig. 4 A are the results of earlier experiments (Pensacola) which were similar in design to that of the dry series in the present study (San Diego) The curves drawn with solid lines compare the mean settings made by nine normal medical students with those made by the normal control subjects *(three) used in this experiment, indicating that the latter* are fairly representative of a larger group

The dashed lines in Fig. 4 A represent settings made under dry conditions by the four L-D participants in this experiment and those made by the larger group of which they are a part. Comparison between means of the settings made by the entire group and by the *group fragment* on the previous occasion (Pensacola) indicates that the settings of the small group were substantially below those of the large group. When the settings made by the small L-D group in Pensacola are compared with those made by them in San Diego, higher values in the present study are seen except when th change in the GIH was 10

Fig. 4 B summarizes all of the findings of the present experiment in terms f group differences between dry and wet conditions in th three normal and four L-D subjects.

COMMENTS

In this experiment an attempt was made to control otolith and nonotolith sensory inputs which might influence the perceived direction of space as indicated by the apparent rotation of a line of light in the dark when the subject was exposed to a change in direction of the gravitoinertial horizontal with respect to himself With regard to nonotolith receptors, stimulation was greatly reduced although not perfectly controlled by immersing the subjects in water up to the neck Otolith inputs could only be controlled by selecting subjects with or without loss of otolith function there was no possible way of reducing the effects of gravitoinertial forces on the field receptors in the vestibule It is important to emphasize that in every experimental trial there was full opportunity for any influences having their origin in the otolith organs to become manifested, whereas there was not the same level of assurance that nonotolith inputs were completely excluded Consequently the lowest values of the settings obtained in any series of trials under water immersion conditions still registered the *maximal* otolith influence These lowest values for the three normal subjects were not far different from their values under dry conditions, with the exception of those of CU where the difference in magnitude under wet and dry conditions was greater than the magnitude of the illusion perceived under dry conditions by the L-D subjects JO and MY and not far below that for PE. Stated differently the demonstration that nonotolith sensory inputs may or may not contribute to the perception of the oculogravic illusion in normal subjects explains at least in part, individual variance in its perception among L-D subjects To the extent that nonotolith contributions (to the illusion) can be demonstrated in normal subjects, they subtract from the need to invoke the phenomenon of compensation to account for the perception of the illusion in L D subjects.

When the L-D subjects were exposed under water immersion conditions, any residual otolith receptors were inescapably stimulated while nonotolith receptor systems were never completely suppressed Under these conditions the lowest values of the settings in the case of JO and MY indicate that they did not perceive the illusion and judged by this test there was not evidence of residual otolith function The comparable "lowest values in the case of PE and ZA indicate that they perceived an illusion but the likelihood that this was due to residual otolith function is small because the absolute values are small inconstant and far below the values under dry conditions

At all events there is proof that nonotolith sensory inputs were mainly or entirely responsible for the perception of the illusion in L D subjects and that the individual variance was great For subject ZA the curves representing settings under dry conditions were similar to the values obtained with normal subjects. Under wet conditions the values were far lower than in the normal controls although still greater than those obtained from L D subjects The likelihood that these large nonotolith values in the case of

ZA would be matched by the nonotolith values of a normal subject would seem to be small based on our findings: it would require a setting of 70 when the force vector was at 30. This small likelihood is supported by the fact that, over the years, ZA has shown a *strong tendency toward marking* higher estimates of the illusion.

The bizarre settings by LI under wet conditions seem to implicate neural connections between the otolith and visual pathways. The small differences between wet and dry conditions suggest that nonotolith sensory inputs were not previously involved. The ranks of the normal and L-D subjects within their groups with respect to their ocular counterrolling index did not have an apparent significance in terms of the perception of the illusion. Among the L-D subjects, JO had the highest value, an index of 170, yet the proof that he had lost all otolith function, as determined by lack of perception of the illusion under immersion conditions, was good. Moreover, as mentioned earlier, among the entire group of L-D subjects he was one of two whose behavioral responses least resembled the normal. If the relatively large compensatory roll of the eyes in his case had its genesis in the otolith organs, then it measures a residuum of function with no easily demonstrable useful purpose.

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ZUSAMMENFASSUNG

Der getrennte und kombinierte Einfluss von Otolith- und Nichtotolithreizen auf die Wahrnehmung der oculogravischen Illusion wurde mit der Veränderung der visuellen Umgebung und des gravito-inertialen Kraftfeldes untersucht. Die visuelle Raumwahrnehmung von vier Marinefliegern und vier tauben Personen mit beiderseitigen Labyrinthdefekten, wenn im Trockenen und in Wasser bis zum Nacken eingetaucht, wurde verglichen. Der Einfluss 1. der Kraftfeldrezeptoren in den Vestibularorganen und 2. der nichtvestibularen Propriozeptoren, die durch unseren Stützkontakt gereizt wurden, konnte unterschieden werden. Es ergab sich unter den verschiedenen Bedingungen, dass fur normale Personen der vestibulare Anteil auf Grund der Richtung des gravitoinertialen Kraftvektors vorhersagbar ist, dass jedoch der nichtvestibuläre Anteil wechselt; er kann relativ gross oder klein sein. In Personen mit beiderseitigen Labyrinthdefekten war ein nichtvestibulare Anteil stets vorhanden, variierte aber stark individuell. Die Bedeutung der Befunde für das Testen der Funktion des Otolithorgans wird diskutiert.

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DEVELOPMENT OF RESPIRATORY TRACT CILIA IN FETAL RABBITS

Electron Microscopic Investigation

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Cilia develop in the respiratory tract of rabbits during the 22–23 days in utero. In the early "pre-cilia" stages, cuboidal cells elongate and develop microvilli on their upper or luminal surface. A large number of basal bodies are produced in the cytoplasm between the nucleus and upper surface. The basal bodies migrate towards the apical surface and orient themselves properly with respect to the surface. Finally a cilium rises above each basal body. Throughout the respiratory tract, this same sequence of steps is followed during ciliogenesis, but the upper part of the airway develops its ciliated epithelium first. The nose is followed by the larynx, then the trachea and finally the bronchi.

We have been unable to locate a published comparison of the time course followed by various parts of the respiratory tract in the maturation of the ciliated epithelium, although the steps of ciliogenesis in any single cell are well described. Mobile cilia (sometimes called "kinocilia" to differentiate them from the non motile cilia of the inner ear known as "stereocilia") are each attached to a "basal body". Before the turn of the century anatomists discovered that basal bodies resembled centrioles and theorized that basal bodies were derived from centrioles. Lenhossek (1898) and Henneguy (1898) independently reported that basal bodies were produced within the cell from centriole division and that each cilium was formed by a basal body after it attached to the upper cell surface. Earlier Henneguy had showed that sperm's tail was similarly produced by a centriole. In 1910 Erhard described development of cilia and flagella in a number of protozoa, in a report with 140 citations from the literature. Details were added through the work of Ikeda (1906) in various human specimens, Helvestine (1921) in mussels, and by Renyi (1924). Saguchi (1917) wrote an interesting account of the history of the study of cilia which credited de Heide

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with the discovery of ciliary movement in 1683 and was a critique of the Henneguy and Lenhossek theory Leeson (1961) was the first to report use of the electron microscope to study ciliogenesis in the respiratory tract and his results confirmed the Henneguy–Lenhossek concept Better resolution provided by the electron microscope made it possible to show that each basal body is identical to a centriole in its fine structure He was able to show that cilia did not begin to appear at the cells upper surface until the basal bodies had been produced deep within the cell and had migrated up to the upper surface Microvilli were mentioned as a previous stage of cilia Electron microscopic observations during the development of human nasal cilia were reported by Ewert (1965) in a comprehensive study of the function of cilia in the nose of healthy and diseased subjects Regeneration of ciliated epithelium after trauma has been studied with light microscopy by A C. Hilding (1965) and by Burian & Stockinger (1957 and 1963) and D A Hilding & A C. Hilding (1966) with the aid of the electron microscope The electron microscopic appearance of cilia at different phases during the beat cycle has been elegantly described by Satir (1963) and the details of each cilium by Rhodin (1966) Early electron microscopic studies of cilia were published by Brown (1945) Jakus & Hall (1946) Engstrom (1951) and Engstrom & Wersäll (1952)

The purpose of this paper is to add further details to the electron microscopic description of ciliogenesis and to show the sequence of ciliary maturation in various areas of the respiratory tract of rabbits.

MATERIALS AND METHODS

Rabbit fetuses were delivered by Caesarian section at 22 25 28 days after conception Newborn and adult animals were used for comparison As soon as possible after death, specimens were selected from the nose larynx trachea and bronchi and placed in cacodylate buffered 5% glutaraldehyde, then sub-divided into smaller pieces. After thorough washing in buffer the specimens were post fixed in buffered 1% osmium tetroxide dehydrated and imbedded in Epon (Luft 1961) Sections were cut free hand with a

FIGS. 1–4 Illust ati g th sequ nce of ent which i foll wed duri g m turati of ciliated pithelium Th proces begins, nd is complet d ll t i th ose th n in the larynx, trachea and f ally th bronchi Phase-contrast light micrographs.

FIG. 1 Pre-cilia" stage The upper surf ce of ach c ll i d mesh ped nd smooth, as seen with the light microscope N goblet cell re prese t Bronchi l pithelium 22 days.

FIG. 2. First cilia appear N g blet lls. Th nasal pithelium passes this t g bef re 22 d ys, trache l by 25 days and th bronchial reaches it t 28 da Lary g al pith li m 25 days.

FIG. 3. Cilia well-developed. No gobl t cell Laryng l pith li m at 28 days.

FIG. 4. Mature epithelium with goblet ll and cilia Nasal pithelium, newborn.


1


2


3


4



FIG 5 "Pre-cilia" stag Laryngeal epithelium at 22 days. There re sh rt microvilli n the uppe surface f th stumpy columnar ells. Th re are a few dark cells (*D*) scattered through thi two-lay r pithelium th t appear t be future g bl t cell Basement membrane (*BM*) Electron micrograph, 8500

razor blade for phase-contrast light microscopy and with an LKB Ultrotome for examination with an RCA EMU 3G electron microscope A saturated solution of uranyl succinate in 50% alcohol was used to enhance contrast of sections

RESULTS

Cilia develop first in the upper part of the respiratory tract then appear at lower levels As seen in Figs. 1–4 cilia were seen earliest in the nasal mucosa, then in the larynx, and finally in the trachea and bronchi The first cilia were found in the nasal epithelium by the 22 day stage and the entire respiratory tract was ciliated by 28 days



FIG. 6. "Pre-ciliary stage" basal body formation. Nasal epithelium, 22 days. Cell on left shows cluster of small, faintly staining basal bodies during early step in their multiplication. Notice that each of the basal bodies in the cell on the right is accompanied by prominent dark "basal foot". Electron micrograph, 34,000.

FIG. 7. Higher magnification of marked area. 82,000.

FIG. 8. Higher magnification of marked area in Fig. 6. 72,000.



FIG. 9 Early tage of basal body formati n near nucleus (N) Each basal body has ine tripl mi rotubules × 165,000

Identical stages were followed in the production of cilia by the cells from all locations although the process began and finished earlier at upper levels. Fig 5 is a low power electron micrograph that illustrates the early "pre-cilia" stage. Two or more layers of cuboidal cells rest on a basement membrane. The upper or luminal surface is dome-shaped and covered by small microvilli. Occasional cells with dark nuclei and cytoplasm were found They are probably the early stage of goblet cell formation

The second stage of basal body production is illustrated in Figs. 6–8 Two neighboring cells show slightly different phases On the left a few small hazy basal bodies have formed in a cluster A pairing relationship seems to prevail In the cell on the right the basal bodies have reached mature size and their details are more obvious Often a black staining



Fig. 10. Pre-cilia stage Bronchus, 25 days. A few cilia are beginning to push up through the [illegible] cell surface. Electron micrograph, 4500.

Fig. 11. Higher magnification same specimen. There is no evidence that cilia are being formed from previously existing micro villi.







FIG 12 Tw nty two day nasal pith lium. Cilliog nc is l more ad nced in th nose than elsewhere. 8400

FIG 13 Solitary cilium in 22 day nasal mucous m mbran (a w) Mo t cells simultaneously produce many ilia but occasi nally this unusual pattern i fou d i immature pithelium 10,300

FIG. 14 High r magnification of solitary lubbed ili m. The basal body i not ppare t becaus of th plan of th secti n 112,000

sphere was found near the "end" of the basal body cylinder In some cases it was attached near the side, with a resemblance to a 'basal foot" It was tempting to wonder if these could be buds" of future basal bodies and if this figure actually depicts basal body replication The early basal bodies are formed near the nucleus (Fig 9) Each consists of nine triple microtubules

The next stage is the ascent of basal bodies through the cytoplasm to the upper surface orientation perpendicular to the surface, then beginning



Fig. 15. Laryngeal epithelium, 25 days. Some patches f cell re almost completely ciliated at this stag I the larynx. ×200.

Fig. 16. Higher mag ification showi g basal bodies clustered at t p of cell with be ginning formation of cilia. sal foot (*F*) Cross cut shafts abov belong t another cell, when f llowed through serial sections. ×25,000.

growth of cilia (Figs. 10 and 11) Although not illustrated here the basal bodies ascend as a group Often we found a zone free of basal bodies between the upper surface and the ascending group that gave us the im pression that there may be a pause for proper alignment before the final move t the top We have been unable to find a cilium forming within a microvillus and are now inclined to believe that cilia arise at the point of contact by the basal body with no particular reference to previously existing microvilli.

A single cilium can occasionally be found arising alone from a cell with only micro illi (Figs. 13 and 14) The illustrated example is a peculiar club-shaped cilium It seems likely that this phenomenon is more closely related to the type f cilium formation that occurs elsewhere, for instance in th inne ear Each cell facing endolymph, whether of the future stria scularis, Reissners membrane or organ of Corti, has a single kinocilium (Kikuchi & Hilding, 1966) Often these cells also have a number of microilli.

Figures 15 nd 16 illu trate the final stage f ciliogenesis when most cells h e mature-looking cilia, but a few are still in the process of produc ing cilia. Th cell have become quite tall, and their mitochondria have become concentrated in their upper portion.

Mature ciliated cells have microvilli as well s cilia (Fig 18) Micro-



FIG. 17 Early goblet cell (G) Ciliated cell ppea mature Baseme t m mbra (BM)



Fig. 18. Adult ciliated epithelium from trachea showing beat cilia with basal bodies, several with "basal foot" (F). Microvilli between cilia are sometimes branched.

villi sometimes branch, and are often nearly as long as the cilia. Figure 19 is a composite which illustrates the major features of each cilium from its basal body and basal foot through its shaft to the tip.

We found a few dark cells (Figs. 5 and 17) scattered through the *epithelium at every stage. Because their cytoplasm resembles* that of goblet cells, we believe they represent a precursor stage.

DISCUSSION

Centrioles replicate themselves during cell division while they act in some mysterious way to help orient the strands of chromatin as they divide. During ciliogenesis they reproduce themselves hundreds of times forming basal bodies, find their way to the upper cell surface, and then emit a pair of microtubules from each triplet of the basal body. They must have special protein synthesis mechanisms and contain substances fundamental to cell organization. They remain fascinating enigmas.

We had hoped that intensive study of the early stages of ciliogenesis in the fetus would yield some clues about centriole replication. We found a few examples of early basal body formation, as seen in Figures 6 and 7 that suggested that they do increase in size after first appearing. Often

they occur in pairs and commonly are oriented at right angles to each other suggesting that new one emerges from the side of the parent

The large homogeneous cilia that are found in regeneration of ciliated epithelium after trauma are not present during ciliogenesis in utero In other respects the two processes are identical

The nucleus and cytoplasm of goblet cells is darker than that of ciliated cells In immature epithelium scattered cells have the same kind of dark cytoplasm and nucleus and we believe can be identified as goblet cell precursors We have found no evidence that ciliated cells can change into goblet cells

It is the general experience of those who have used rabbits as experimental animals that they will survive if they are delivered by Caesarian section any time after the 28th day of gestation but that most will not survive if delivered earlier It is tempting to suggest that ciliated epithelium is important for survival and its maturation must be completed in order for the young rabbit to survive However we have no direct evidence that this concept is correct We have learned that the respiratory tract epithelium of all levels has reached nearly its adult form by the 28th day of gestation.

ZUSAMMENFASSUNG

Cilien entwickeln sich in den Atemwegen von Kaninchen zwischen dem 22 und 28 Tag in utero In den frühen präziliaren" Stadien findet man Elongation von kubischen Zellen und die Formierung von Mikrovilli an ihrer oberen der dem Lumen zugewandten Oberfläche Eine grosse Anzahl von Basalkörperchen entwickelt sich im Cytoplasma zwischen dem Nukleus und der Oberfläche Diese Basalkörperchen wandern gegen die apikale Oberfläche und orientieren sich zu ihr Schliesslich entwickelt sich je ein Cilium über jedem Basalkörperchen Während man die gleiche Folge von Entwicklungsschritten der Cilogenese in der ganzen Ausdehnung des Atemtraktes findet entwickeln sich jedoch die Cilien in den oberen Abschnitten der Atemwege zuerst. Zuerst entwickeln sich Cilien in der Nase, dann folgt die Entwicklung im Kehlkopf Trachea und schliesslich in den Bronchien

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FIG. 19 Adult cilium as seen in l ngitudin l a d cross-section (c mpo it) Tip (*T*) Shaft (*S*) Origin (*O*) with nearby cross-cut micro illi, and basal body (*B*) with basal foot (*F*) Longitudinal section x 12,000 and cross-cut 138,000




T


S


B
19

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ON THE INFLUENCE OF THE RETICULAR ACTIVATING SYSTEM UPON THE AUDITORY FUNCTION

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The aim of the present paper is t summarize the neurophysiological, neuropharmacological, and clinical evide ce which indicate how the reticular formation of the b.s. influences the general processes of integration and particularly the uditory integration. The authors reach the conclusion that the ascending reticular tonic activity may influence the time constant of the sensory integration processes both through a modification of the overall conduction time of afferent impulses along the specific pathways nd through a modification of the operation time of reflex mechanisms acti ted by the sensory input.

A great number of experimental and clinical findings show that there are two control mechanisms of the sensory input. The first type which might be defined as "specific" is formed by the so-called centrifugal or afferent sensory pathways, whereas the other aspecific" type is represented by central nervous system (C.N.S.) levels not being an anatomical part of the different sensory pathways, but related to them by collateral branches.

Neuroanatomical and neurophysiological investigations have shown that there are at least six systems mutually interacting for the elaborations of sensory input (Livingston 1959) i.e (*a*) ascending sensory pathways form ing the classical lemnisci (*b*) ascending pathways connected with neurons f the reticular formation of the brain stem, which diffuse their impulses to the cortex i the ascending reticular projection, (*c*) pyramidal motor pathw ys, (*d*) extra-pyramidal motor pathw ys, (*e*) the brain-stem reticular formation with it ascending influences upon both the cerebral and cerebellar hemispheres, (*f*) the centrifugal sensory control mechanisms.

The dynamics of all these interdepending systems acting simultaneously has been defined as "transaction" thu indicating a more complex mechanism a compared with the rather elementary processes of interaction"

Among these different syst ms, the brain-stem reticular formation plays an important role The aim of th present paper is a review of the most important results obtained by nimal experimentation concerning the reticul r influ nce upon the auditory system these data will be further related to some linical findings.

Experimental Data

The investigation of the reticular influence upon the auditory integration started when alterations of the auditory responses at the cortico-thalamic level were observed depending on the sleep-wakefulness state of the animal. Since these alterations of the auditory-evoked potential persist even if the stimulus parameters remain unchanged, we might assume that they are related to the different functional condition of nervous structures of the thalamus and of the cerebral cortex in the sleep-wakefulness state, which is mainly regulated by the *fluctuations* of the tonic ascending reticular influence.

The main changes are well known: when in an animal the EEG activity shows a transition from a sleep pattern to a pattern of moderate wakefulness, the cortico-thalamic potential evoked by an afferent impulse decreases in latency and waxing and waning of its recovery curve, which is typical of the sleep condition, disappears. This finding has been observed by King *et al.* (1948) in the somesthesic cortex.

At the same time, when the EEG activity is "awakened" an increased amplitude of the response has been shown by Dumont & Dell (1958) and further by Bremer & Stoupel (1959).

Desmedt & La Grutta (1957) reported that when the EEG activity of an animal passes from a pattern of moderate arousal to one of maximal *awakening*, which might be compared in man to an intense emotional activation, the cortical evoked response is clearly depressed.

In the cat, we have registered the potential evoked by a click in the medial geniculate and in the temporal cortical regions and we have been able to show that—during spontaneous transition from wakefulness to sleep—there is an increase of peak latency of the evoked response reaching 1–2 msec. During sleep the recovery curve of the geniculo-cortical excitability shows a typical waxing and waning with a period of about 150 msec; these oscillations disappear as soon as an arousal pattern occurs in the EEG record (Antonelli, 1963).

These phenomena, in agreement with the data reported by King *et al.* (1948), do not take place in the bulbar cochlear nuclei, but are typical of the geniculo-cortical levels.

A number of neurophysiological and neuropharmacological controls indicate that these modifications depend upon the reticular tonic activity level. Actually, we have found that electrical stimulation of the reticular formation brings back the latency values typical of the condition of awakening, whereas electrocoagulation of the reticular formation elicits the same (although quantitatively increased) variations of the auditory response which are characteristic of deep sleep. The peak latency of the response following reticular lesion increases by 2–5 msec (Antonelli, 1963 *a*).

The same aspects of sleep that follow a reticular inactivation can be obtained by the use of drugs which at a certain dosage depress electively the reticular tonic activity, as for instance barbiturates, while other CNS

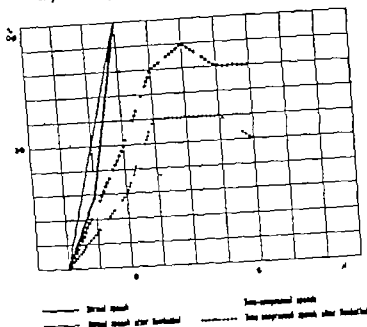


Fig. 1. Effect of single dose f Nembuthal (100 mg) upon the rticulation curv for normal and time compressed peech (350 words/minut) Significant decrease f the discrimination score for time compressed peech only

depressant drugs, such as chloropromazine and meprobamate, have been shown to be inactive (Antonelli, 1963)

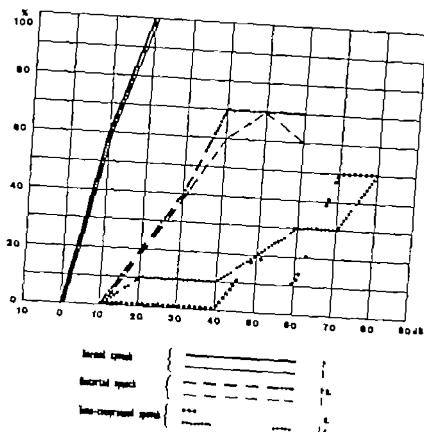
The specific ascending reticular influence upon the sensory integration has further been shown by experiments on the behaviour of unrestrained animals with chronically inplanted electrodes. Fuster (1958) has shown that a slight electrical stimulation of the reticular formation leads to a marked improvement of the ta histoscopic performances in the monkey

The ascending reticular activity appears therefore to be capable of in fluencing the time constant of sensory integrative processes both through a shortening of the conduction time of afferent impulses along the specific pathways and through a modification of the operation time of reflex mechanisms activated by the sensory input.

Experiments in Man

When the threshold f succession between two clicks is measured in man during an EEG recording, a marked reduction of the threshold values may be observed when the task is performed in a state of desyn hronized cortical acti ity (increased ascending reticular influence) as compared to a stat of alpha activity (Antonelli, 1962)

In udiometric practic if the subject is presented with some lists of l w-redundancy sentences, it has been found that in a condition of normal sleepines or after barbiturates administration (100 mg Nembuthal) there



F g. 2. Typical patt rn of the sen iti ed speech tests performance in a case with nucleo-reticular vestibular syndrome of th chronic type Bilateral and se re l s f discrimina tion confined to the time-comp essed peech discriminati n.

exists a significant decrease of the intelligibility of time-compressed sen tences as compared to data obtained by the same subject in a wakeful state (Albano & Antonelli 1963) (Fig 1)

One might assume that this phenomenon derives from a slight obnubila tion of mental conditions due to the sleepy state However this doubt can be discarded as in our case the intelligibility deficit is present only for time-compressed speech whereas psycholectic drugs, such as scopolamine and atropine, leading to a transitory mental obnubilation affect all low redundancy tests (time-compressed filtered interrupted speech tests) to a degree which is obviously proportional to their influence on mental factors (Calearo & Antonelli 1964)

On the other hand it is well known that in old age and in some diseases of the central nervous system such as Parkinson s disease there exists a particular impairment of discrimination for time-compressed speech It has been found that in these subjects, if some psychoanaleptic drugs are given which increase the reticular tonic activity there is a temporal im provement of time-compressed speech discrimination (Blondiau & Bocca, 1959 Antonelli & De Mitri unpublished data)

We know from vestibular pathology those cases where an acute or chronic condition of vertigo is accompanied by a very severe caloric hypo-

reflexia or areflexia. Some authors *believe that the site of the lesion in* such cases is situated in the central vestibular pathways (De Kleyn 1944) and more precisely in the bulbar vestibular nuclei and the *surrounding* reticular formation (Arslan, 1948 Arslan & Sala, 1956 Arslan, 1957)

In a number of these cases, a bilateral, symmetrical impairment of the discrimination for time-compressed speech has been found by Moscaro & *Pignataro* (1964) (Fig. 2) This limited deficit (no other hearing alteration *was present) appears to be directly* related to the reticular vestibular alteration.

CONCLUSIONS

Experimental data indicate that the function *of cortico-thalamic* structures checked by the activating reticular system may act on the sensory cortex, offering a mechanism which is able to influence the central elaboration of afferent impulses.

The experimental data in man and the audiometric findings in patients with nucleo-reticular syndrome confirm the existence of a reticular control of auditory integration and point to its diagnostic value.

We might deduce that a lesion of the brain stem reticular formation causes a decrease *of the ability for temporal discrimination* of auditory messages.

The deficit of discrimination for time-compressed speech in patients with *bulbopontine* reticular *lesions* might therefore *offer* an interesting clinical proof of the lesion of one of the mechanisms of auditory transaction

ZUSAMMENFASSUNG

Zweck dieser Arbeit ist eine Zusammenfassung der neurophysiologischen, neuropharmakologischen und klinischen Befunde die den Bew is liefern, dass die Substantia reticularis des Hirnstamms die allgemeinen Integration vorgänge und insbesondere die Gehörintegration beeinflusst. Die Verfasser gelangen zum Schluss, dass *die aszendierende* retikuläre tonische Aktivität die Zeitkonstante der sensori llen Integrations *vorgänge* durch ein Veränderung der Übertragungs *eit der afferenten Impulse längs d spezifischen* Bahnen sowie durch eine Veränderung *der Zeit der reflektorische Mech nismen* die durch die sensorielle Zufuhr akti iert wird, beeinflusst.

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ULTRASONIC CLEANER FOR OPERATING ROOM USE

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By means of a removable insert which may be sterilized, an ultrasonic cleaner for operating room use has been found practical. Used in connection with oto-surgery such as tympanoplasty and free-laying of the semicircular canals prior to ultrasonic irradi ti n, tc., it cleans burrs, drills, curettes and other instruments from bon chips as w ll as coagulated blood.

A small, high intensity ultrasonic cleaning unit has found application in our operating room for the cleaning of drills, burrs, and curettes as well as other instruments used in connection with oto-surgery such as tympanoplasty stapes surgery free-laying of the semicircular canals prior to ultrasonic irradiation in the treatment of Menière s disease (Sjöberg *et al* 1963) etc. Since the necessity of maintaining sterile conditions is at all times present, the instrument was designed to make this possible.

The basic unit employed is an ultrasonic cleaning unit of high intensity which was originally designed to solve the cleaning problems of the instrument and jewellery fields where the elimination of buffing and polishing compounds from intricate details is generally difficult and time consuming. For use in the operating room we have designed a special wide flanged trough (A) which may be sterilized and set down into the cleaning tank of the ultrasonic unit (B) Ultrasonic coupling is accomplished through a small amount of liquid in the bottom of the tank, the inserted trough having been designed to make contact at just the level which insures maximum effect.

The main requirement for good cleaning action is a high degree of ultrasonically induced cavitation in the bath The term cavitation, as applied to ultrasonic treatment, has come to include the sequence of events from the formation of microscopic vapor phase bubbles during the negative pressure portion of the ultrasonic wa e, to their collapse with rising pressure, and the resultant highly localized, but extremely intense, shock waves resulting from their collapse It is mainly these shock waves which account for the ability of ultrasonic cleaning baths to eliminate contamination and embedded particles from crevices and hollows as well as smooth surfaces.

Although the most effective cleaning is done with the combination of

The instrument discussed is a ailable thro gh Ultrapoint, P.O. 212, Uppsala, S eden.

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ZUSAMMENFASSUNG

Ein Ultraschallgerät mit sterilisierbarem Einsatz wurde erfolgreich zur keimfreien Reinigung von chirurgischen Instrumenten angewandt. In der Ohrenchirurgie z. B. bei Tympanoplastik oder bei Freilegung der Bogengänge für Ultraschallbestrahlung, können Schleifscheiben, Bohrer und Küretten auf einfache Weise von Knochensplittern und koaguliertem Blut gereinigt werden.

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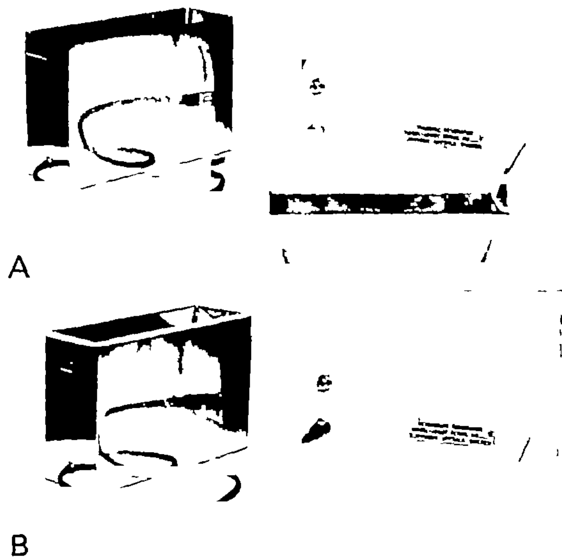


FIG. 1 Th ultrasonic cl aner showing removale trough (A) inserted in cl ni g tank (B)

ultrasound and a cleaning agent or solution specifically suited to the kind of deposit to be removed the need for any instrument in the operating room to be ready for immediate reuse during an operation that is to say sterile as well as clean, precluded the use of any special cleaning agents Instead the ultrasonic bath has been made up of physiological saline solution—which incidentally is always at hand in the operating room

The instrument itself consists of a transistorized generator delivering 40 watts of electrical energy at 32 kHz to a sandwich type aluminum barium titanate-aluminum transducer bonded to the bottom of a rectangular trough approximately 60 × 200 × 50 mm Automatic tuning and a fixed out put level eliminate all need for any adjustment during use Thus, any nurse or operating room assistant can use the instrument without previous special training

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NOBEL SYMPOSIUM X

Disorders of the Skull Base Region

Stockholm, August 13–16, 1968

Tuesday August 13

18.00–20.00 Registration

18.30–21.00 Reception

Wednesday August 14

Morning session

Professor *T. Sjöstrand*, Dean of the Medical Faculty of the Karolinska Institute

Professor *C. A. Hamberger*

Welcome and opening address

ACOUSTIC NEUROMA I

Moderator: *Jongkees, L. B. W.*

Olivecrona, H. Introduction

Engström, H. Anatomy of statoacoustic nerve

Grepe, A. Normal anatomy of the cerebello-pontine angle as studied radiologically

Aschan, G. Diagnosis of vestibular system disorders

Discussion

Coffee

Kleckhoff, J. Audiologic diagnosis of acoustic neuroma

Anderson, H. Intraaural reflexes in retro-cochlear lesions

Greitz, T. Roentgenological diagnosis in acoustic neuroma

Brunner, S. Tomography in acoustic neuroma diagnosis

Lendin, S. Liquor diagnosis in cases of acoustic neuroma

Moberg, A. Histopathology of the acoustic nerve

Glasscock, M. E. Endarterectomy of the carotid artery within the temporal bone – Movie

Discussion

Moderator's summary

Lunch

Wednesday August 14

Afternoon session

ACOUSTIC NEUROMA II

Moderator: *Norlén, G.*

House, W., Transtemporal bone microsurgical removal of acoustic neuromas I

Hitselberger, W., Transtemporal bone micro-surgical removal of acoustic neuromas II

House, W., *Hitselberger, W.*, Transtemporal bone microsurgical removal of acoustic neuromas – Movie

Coffee

Lundberg, N. Result of total and subtotal removal of acoustic neuromas

Fisch, U. Surgical anatomy of the so-called internal auditory artery

Fluur, E. Exploration of internal auditory meatus in acoustic neuroma

Discussion

Moderator's summary

Thursday August 15

Morning session

PITUITARY FUNCTION AND PITUITARY SURGERY

Moderator: *Bateman, G.*

Wersäll, J. Anatomy of the pituitary gland

Hammer, G. and *Rådberg, C.* Roentgenological anatomy of the sphenoidal sinus

Luft, R., Surgical endocrinology of the pituitary

Angell James, J. Transsphenoidal approach to the pituitary

Luft, R., Pituitary ablation in diabetes mellitus

Discussion

Coffee

Burian, K., Transsphenoidal hypophysectomy – Movie

Escher F Remission in dependence of the hormonal elimination in hypophysectomy of breast cancer
Miller T Hypophysectomy in mammary carcinomas
Moberger G Pharyngeal hypophysis following hypophysectomy
Discussion
Moderator's summary
Lunch

Thursday August 15
Afternoon session
PITUITARY TUMOURS
Moderator *Riskaer N*
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(2) Flumidin — samlade erfarenheter med ABOB, AB Kabi, Stockholm 1965 p. 8 (90 pages, partially in English, available upon request from AB Kabi, Stockholm 3).

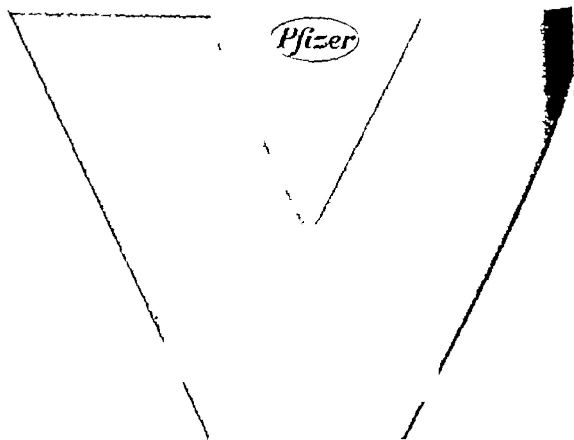
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